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THE WESTERN Journal of Medicine

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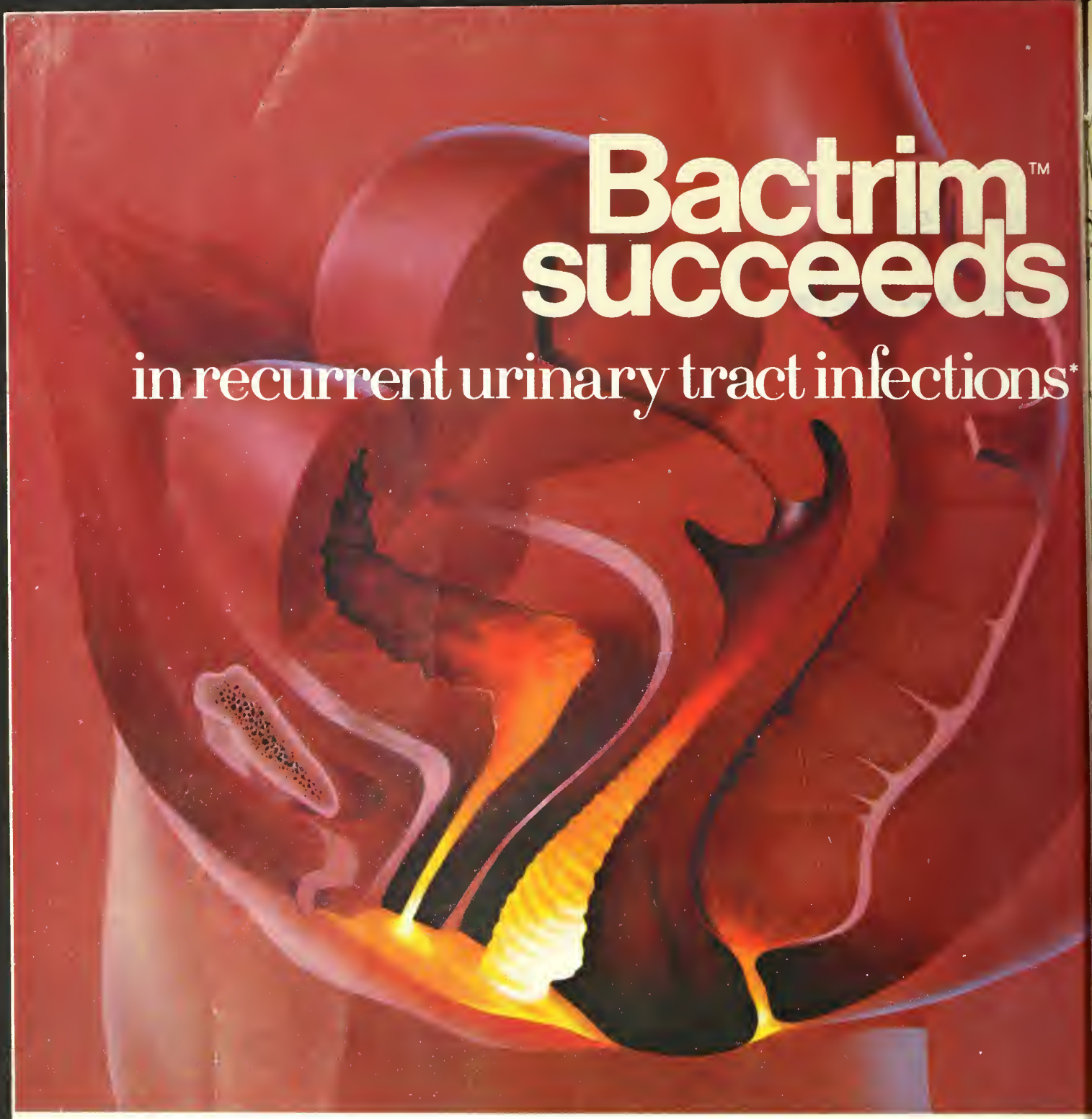

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Bactrim reaches effective levels in urine, serum and renal tissue,[1] to combat infection throughout the urinary tract. The trimethoprim component enters vaginal secretions in therapeutic concentrations,[1] to prevent colonization of bacteria in the periurethral area, probably the major etiologic factor in recurrent UTI.[2,3] And in the fecal flora, Bactrim eradicates Enterobacteriaceae with no resulting emergence of resistant organisms and without adverse effect on the normal intestinal flora.

*due to susceptible *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *P. vulgaris* and *P. morganii*

ata from 231 hospitals, compiled by an independent bacteriologic monitoring service, show:

More isolates of more common uropathogens sensitive to Bactrim than to any other frequently prescribed antimicrobial

r cent of isolates of common uropathogens sensitive to Bactrim and to other antimicrobials

	E. coli	Klebsiella pneumoniae	Proteus mirabilis	Proteus vulgaris	Proteus sp.	Enterobacter sp.	Enterobacter aerogenes	Enterobacter cloacae
Bactrim SMX/SMX	96% (345637)	89% (74499)	94% (64231)	81% (4589)	88% (2317)	92% (2640)	93% (8441)	94% (15882)
MPICILLIN	74% (368815)	4% (80911)	87% (69927)	17% (5005)	43% (2460)	18% (3022)	7% (8727)	11% (16923)
PHA-XIN* FACLOR*	81% (367535)	87% (80388)	92% (69681)	13% (4970)	48% (2381)	25% (2968)	16% (8886)	7% (16800)
TROFUR-ITOIN	96% (346033)	68% (75222)	8% (67011)	16% (4634)	12% (2141)	75% (2782)	61% (8008)	71% (15783)
TRACY-LINE	74% (357548)	80% (77150)	4% (69173)	32% (5018)	20% (2278)	82% (2467)	84% (8329)	77% (16128)

Numbers in parentheses indicate projected number of isolates tested with antibacterial.
Source: BacData Medical Information Systems, Inc., Summer 1980.
*Tested with cephalothin disc, recommended as representative of all cephalosporins

Bactrim consistently proves its *in vitro* effectiveness against the organisms estimated to cause 90-95% of urinary tract infections: *E. coli*, *Proteus mirabilis*, *Klebsiella* and *Enterobacter* species.[4,5] Susceptibility tests are believed to correlate more closely with clinical results in urinary tract infections than in any other kind.[4]

No significant change seen in resistance patterns

Uropathogens sensitive to Bactrim have demonstrated no significant increased resistance *in vitro* after many years of use in patients with urinary tract infection.[6] In one study,[7] SMX/TMP (Bactrim), given over a period of four weeks, was not followed by emergence of resistant strains of Enterobacteriaceae—a result noted to correlate with clinical findings that in patients given SMX/TMP, urinary tract reinfections with resistant organisms are rare.

It is important to maintain adequate fluid intake during therapy. Bactrim is contraindicated during pregnancy at term, the nursing period, in patients hypersensitive to its components, and in infants under 2 months of age.

References. **1.** Rubin RH, Swartz MN: *N Engl J Med 303* 426-432, Aug 21, 1980. **2.** Dhalla S, Flynn JT: *NY State J Med 80*: 1087-1094, June 1980. **3.** Stamey TA: *J Urol 109* 467-472, Mar 1973. **4.** Kunin CM: *Detection, Prevention and Management of Urinary Tract Infections*, ed 3. Philadelphia, Lea & Febiger, 1979, pp. 91, 140. **5.** Mayer TR: *Geriatrics 35*: 67-77, Mar 1980. **6.** BacData Medical Information Systems, Inc., Winter 1976-1977 to Summer 1980. **7.** Knothe H: *Infection 7* (Suppl 4): S321-S323, 1979

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Please see summary of product information on following page.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides, patients with documented megaloblastic anemia due to folate deficiency, pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus, infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended, therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy:* Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

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Use in ambulatory patients: Empirin with Codeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with other central nervous system (CNS) depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with Empirin with Codeine may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Use in pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, Empirin with Codeine should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS:

Head injury and increased intracranial pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions: The administration of Empirin with Codeine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Allergic: Precautions should be taken in administering salicylates to persons with known allergies; patients with nasal polyps are more likely to be hypersensitive to aspirin.

Special risk patients: Empirin with Codeine should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture, peptic ulcer, or coagulation disorders.

ADVERSE REACTIONS: The most frequently observed adverse reactions to codeine include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus.

The most frequently observed reactions to aspirin include headache, vertigo, ringing in the ears, mental confusion, drowsiness, sweating, thirst, nausea, and vomiting. Occasional patients experience gastric irritation and bleeding with aspirin. Some patients are unable to take salicylates without developing nausea and vomiting. Hypersensitivity may be manifested by a skin rash or even an anaphylactic reaction. With these exceptions, most of the side effects occur after repeated administration of large doses.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. Empirin with Codeine is given orally. The usual adult dose for Empirin with Codeine No. 2 and No. 3 is one or two tablets every four hours as required. The usual adult dose for Empirin with Codeine No. 4 is one tablet every four hours as required.

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References—References should conform to the following order: name of author, title of article, name of periodical, and volume with inclusive pages, month and year—i.e., Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

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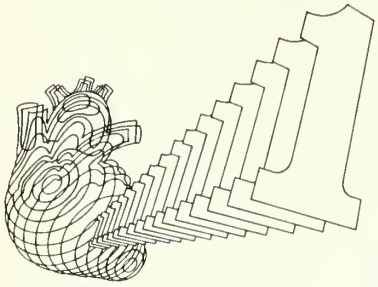

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

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Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses Myocardial infarction and stroke reported with use of this class of drugs) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e g , operating machinery, driving).
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment Amitriptyline component may block action of guanethidine or similar antihypertensives Concomitant use with other psychotropic drugs has not been evaluated: sedative effects may be additive Discontinue several days before surgery Limit concomitant administration of ECT to essential treatment See Warnings for precautions about pregnancy Limbitrol should not be taken during the nursing period Not recommended in children under 12
In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue
Endocrine Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.
Other Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive I V administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime Single *h.s* dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required Limbitrol 5-12 5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12 5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50

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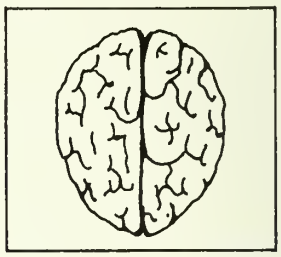
PRESENTS



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H.R. Tyler, M.D., Professor of Neurology, Harvard Medical School, Boston, Mass.

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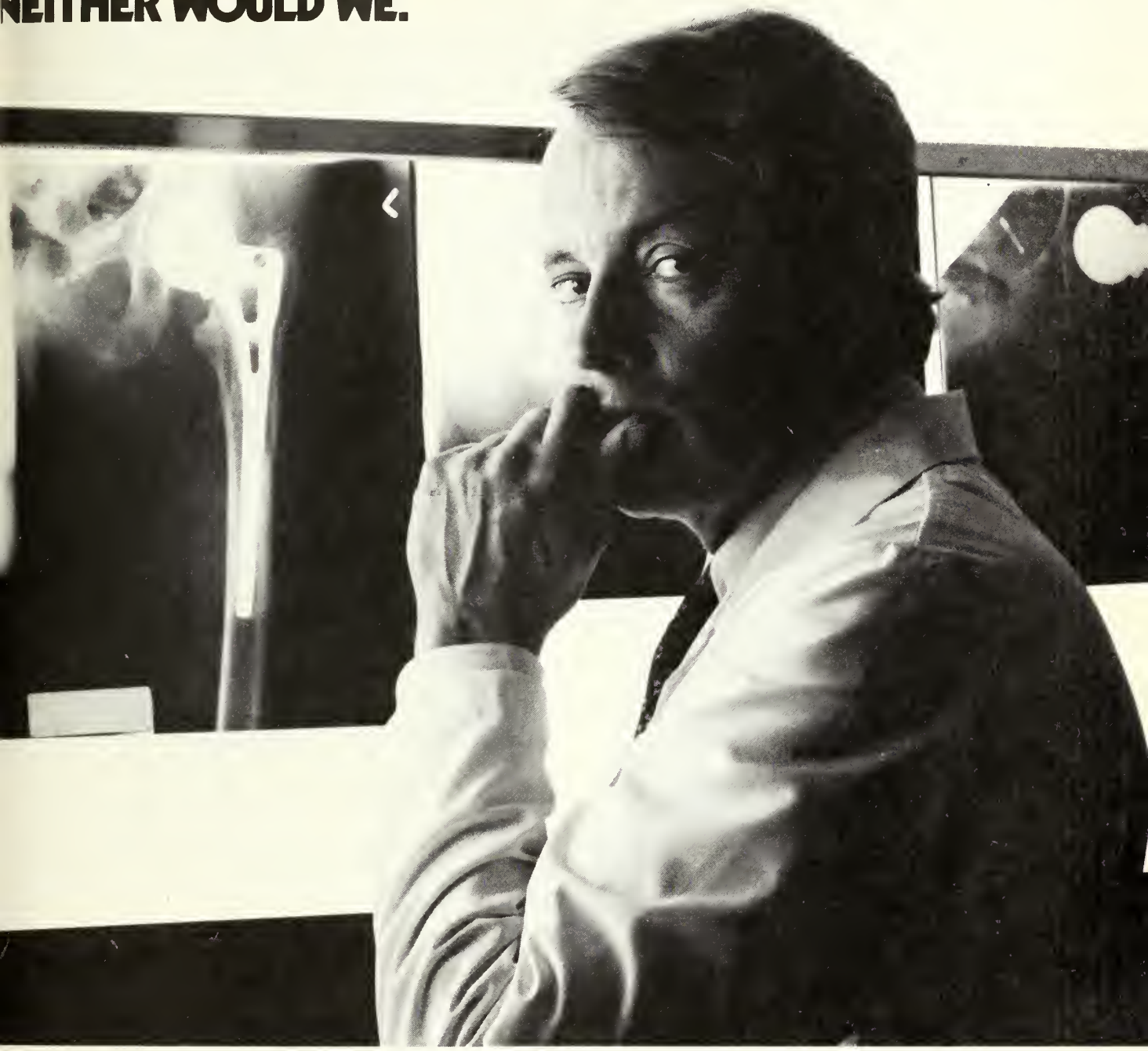

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BRAND OF

CONJUGATED ESTROGENS TABLETS, U.S.P.

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade [4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13.9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose [3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] if therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form ot vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures [7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects [13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows.

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens [19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility [18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens [17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement [19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction [23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users [31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives [33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown [35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives [36] Increased blood pressure may occur with use of estrogens in the menopause [37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression [23a] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen.

a Increased sulfobromophthalein retention

b. Increased prothrombin and factors VII, VIII, IX, and X decreased antithrombin 3. increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e. Decreased pregnanediol excretion

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (*e.g.* three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K, *et al* N Engl J Med *293* 1167-1170, 1975 2 Smith, D C, *et al* N Engl J Med *293* 1164-1167, 1975 3 Mack, T M, *et al* N Engl J Med *294* 1262-1267, 1976 4 Weiss, N S, *et al* N Engl J Med *294* 1259-1262, 1976 5 Herbst, A L, *et al* N Engl. J Med *284* 878-881, 1971 6 Greenwald, P, *et al* N Engl J Med *285* 390-392, 1971 7 Lanier, A, *et al* Mayo Clin Proc *48* 793-799, 1973 8 Herbst, A, *et al* Obstet Gynecol *40* 287-298, 1972 9 Herbst, A, *et al* Am J Obstet Gynecol *118* 607-615, 1974 10 Herbst, A, *et. al* N Engl J Med *292* 334-339, 1975 11 Stafl, A, *et al* Obstet Gynecol *43* 118-128, 1974 12 Sherman, A I, *et al* Obstet Gynecol *44* 531-545, 1974 13 Gal, I, *et al* Nature *216* 83, 1967 14 Levy, E P, *et al* Lancet *1* 611, 1973 15 Nora, J, *et al* Lancet *1* 941-942, 1973 16 Janerich, D T, *et al* N Engl J Med *291* 697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290* 15-19, 1974 18 Hoover, R, *et al* N Engl J Med *295* 401-405, 1976 19 Daniel, D G, *et al* Lancet *2* 287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group J Urol *98* 516-522, 1967 21 Bailar, J C Lancet *2* 560, 1967 22 Blackard, C, *et al* Cancer *26* 249-256, 1970 23 Royal College of General Practitioners J R Coll Gen Pract *13* 267-279, 1967 23a Royal College of General Practitioners Oral Contraceptives and Health, New York, Pitman Corp, 1974 24 Inman, W H W, *et al* Br Med J *2* 193-199, 1968 25 Vessey, M P, *et al* Br Med J *2* 651-657, 1969 26 Sartwell, P E, *et al* Am J Epidemiol, *90* 365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women N Engl J Med *288* 871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women. J A M A *231* 718-722, 1975 29 Mann, J I, *et al* Br Med J *2* 245-248, 1975 30 Mann, J I, *et al* Br Med J *2* 241-245, 1975 31 Inman, W H W, *et al* Br Med J *2* 203-209, 1970 32 Stolley, P D, *et al* Am J Epidemiol *102* 197-208, 1975 33 Vessey, M P, *et al* Br Med J *3* 123-126, 1970 34 Greene, G R, *et al* Am J Public Health *62* 680-685, 1972 35 Coronary Drug Project Research Group J A M A *214* 1303-1313, 1970 36 Mays, E T, *et al* J A M A *235* 730-732, 1976 37 Pfetter, R I, *et al* Am J Epidemiol *103* 445-456, 1976

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(Continued from Page 19)

day-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 18-20—**Pediatric Emergencies.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 25-29—**Controversies and Problems in Emergency Medicine.** UCSD. Monday-Friday.

MEDICINE

July 18-25—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 23 hrs. $295.

July 31-August 4—**Internal Medicine Update.** American College of Physicians at Kihei, Maui, Hawaii. Friday-Tuesday. Contact: ACP, 4200 Pine St., Philadelphia 19104.

August 7-8—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 12-15—**Workshop in Medical Mycology/Dermatomycology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Wednesday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** See Psychiatry, August 15-21.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 25-June 29—**Seminars in Nephrology.** USC at Holiday Inn, Los Angeles/Westwood. Tuesday evenings; five sessions. 12½ hrs. $70.

September 5-8—**Advances in Internal Medicine.** UCSD. Saturday-Tuesday.

September 5-9—**Dermatopathology.** UCD at Silverado Country Club, Napa. Saturday-Wednesday.

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 12-13—**Severe Asthma: State of the Art for the Specialist.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Traci Drelen, LACMA, 1925 Wilshire Blvd., Los Angeles 90057.

September 14-17—**Current Concepts, Controversies and Clinical Strategies in Gastroenterology.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Beverly Hills. Monday-Thursday. 27 hrs. $450. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., Rm. 2049, P.O. 48750, Los Angeles 90048. (213) 855-5547.

September 18—**Diabetes and the Kidney—14th Annual Symposium on Renal Disease.** National Kidney Foundation of Northern Calif. at Hilton, San Francisco. Friday. $60. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd., Burlingame 94010. (415) 697-0110.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 24-26—**Office Dermatology.** STAN. Thursday-Saturday. 19 hrs. $275.

September 25—**Hypertension.** UCD. Friday.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 3-10—**Cardiology—1981.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $350.

October 6-7—**48th Annual Fall Symposium and 13th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $125, AHA member; $150, nonmember. Contact: Mary Frances Flynn, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 7-9—**Current Neurology.** Straub Clinic and Hospital at Honolulu Art Academy, Honolulu. Wednesday-Friday. 12 hrs. $175. Contact: Office of Medical Administration, Straub Clinic and Hospital, 888 S. King St., Honolulu 96813.

October 9-11—**California Society of Internal Medicine—Annual Meeting.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 12-16—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs.

October 14—**Thrombophlebitis and Thromboembolic Disease.** LLU. Wednesday. 4 hrs.

October 14-December 16—**Nephrology.** UCLA. Wednesday evenings.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 17—**Pediatric Allergy: Principles and Management.** See Pediatrics, October 17.

October 17-24—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 19-22—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Mark Hopkins Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

(Continued on Page 34)

Limiting the clinical complications of serious intra-abdominal infections

Acute appendicitis

In virtually all intra-abdominal infections, there is a recurring group of three anaerobes that are seen either singly or in combination, often mixed with aerobes.

This triad, composed of *Bacteroides fragilis*, clostridia, and anaerobic cocci (particularly peptostreptococci and peptococci) may complicate perforating appendicitis, abdominal trauma, and penetrating wounds.

Complications of *B. fragilis*

Complications such as thrombophlebitis, intra-abdominal abscess, and wound dehiscence may be explained by unique virulence factors elaborated by *B.fragilis*—the anaerobe most frequently encountered in anaerobic bacteremia and intra-abdominal sepsis.

Specific virulence factors

A capsular polysaccharide on the outer membrane of *B.fragilis* appears to differentiate it from other *Bacteroides* species. Experiments in animals have demonstrated that this polysaccharide alone can cause abscess. Other virulence factors produced by *Bacteroides* are heparinase and collagenase, which contribute to thrombophlebitis and wound dehiscence. Additional virulence factors that may enhance the pathogenicity of *B.fragilis* are lipases, proteases, nucleases, β-lactamases, and superoxide dismutase.

Clinical complications: penetrating abdominal wounds

In a prospective, randomized study at Cook County Hospital, Chicago, 100 patients who had penetrating abdominal wounds with spillage of bowel contents were given kanamycin (0.5 g q12h) and either clindamycin (600 mg q6h) or cephalothin (3 g q6h).[1] The clindamycin/kanamycin-treated group showed significantly fewer episodes of septicemia or intra-abdominal sepsis (see Table 1). The higher complication rate in the cephalothin/kanamycin group was the result of infections due to

Intestinal anastomotic leak

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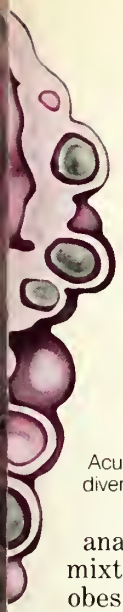

Acute colonic diverticulitis

anaerobic bacteria alone or a mixture of aerobes and anaerobes (see Table 2).

The cost of morbidity

B.fragilis was associated with complications in a majority of 335 patients with perforating appendicitis.[2] A retrospective review showed that these complications caused longer and more costly hospital stays and greater morbidity.

Limiting complications

In intra-abdominal infections, these data suggest that early, aggressive treatment with an antibiotic effective against anaerobes—especially against *B.fragilis* with its unusual virulence factors—may decrease morbidity and limit potentially life-threatening complications.

Thadepalli H, et al. Abdominal trauma, anaerobes, and antibiotics. *Surg Gynecol Obstet* 137:270-276, 1973.

Scher KS, Coll JA: The continuing challenge of perforating appendicitis. *Surg Gynecol Obstet* 150:535-538, 1980.

See next page for brief summary of prescribing information.

Table 1.—Septic Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Septic complications		
Septicemia	7	2
Intra-abdominal abscesses	7	3
Total complications	14	5

*Adapted from Thadepalli et al.[1]

Table 2.—Number of Anaerobe-Associated Infectious Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Mixed aerobes and anaerobes	6	0
Anaerobes	5	1
Totals	11	1

*Adapted from Thadepalli et al.[1]

†Dosage was 3 g cephalothin I.V. q6h and 0.5 g kanamycin I.M. q12h or 600 mg *Cleocin Phosphate* I.V. q6h and 0.5 g kanamycin I.M. q12h.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued (see WARNING box). A summary of prescribing information for *Cleocin Phosphate*—used in the treatment of serious infections due to anaerobic pathogens—can be found on the following page.

In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

Upjohn

Cleocin Phosphate™ STERILE SOLUTION
(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:
clindamycin phosphate
equivalent to ..... 150 mg
clindamycin base
benzyl alcohol ..... 5 mg
disodium edetate ..... 0.5 mg
water for injection ..... qs
When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported, no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. *Musculoskeletal:* Rare instances of polyarthritis have been reported.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription. MED B-8-S

The Upjohn Manufacturing Company
Barceloneta, Puerto Rico 00617

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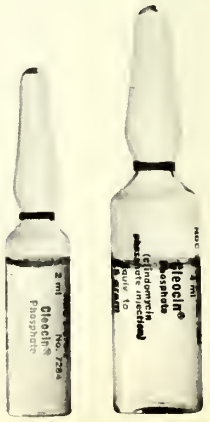
In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION
(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE



J-8809

(Continued from Page 18)

PHYSICIANS WANTED

INTERNIST: Board Certied or eligible internist, to join well-established 3-man group of internists in San Jose, California. Office near excellent general hospital. Guaranteed salary first year. Incremental partnership thereafter. Send CV to Box 6196, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SURGEON & FP NEEDED: Multispecialty Clinic (Surgeons, Internists, FP's) in rural, mountainous area of northern Idaho is looking for a General Surgeon and a Family Practice physician. Contact Dr. Fitz (208) 784-1141.

COLORADO EMERGENCY MEDICINE: Directorship and Clinical positions available in Northeastern portion of the state in moderate volume emergency department. Hourly quarantee plus compensation for Director's added responsibilities. Paid professional liability insurance end other amenities. For further information contact William Salmo toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

NEW MEXICO—NORTHWESTERN: Opportunity available for a physician interested in providing primary care in this modern clinic open 8 a.m.-5 p.m., Monday-Friday. Guaranteed income, liability insurance provided. For details, send credentials to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903; or call toll-free 1 (800) 525-3681 (in Colorado call collect (303) 471-4981).

CALIFORNIA, SAN JOSE: Experienced Emergency Physician with Spanish-speaking ability preferable, wanted to join our group practicing in San Jose at a University-affiliated medical center and two community hospitals. Total patient volume of 90,000; fee-for-service compensation. If interested, send CV or contact: James B. Lane, MD, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Phone (408) 293-8881.

CALIFORNIA, SAN JOSE: Primary Care Physician with experience in minor trauma and Peds. wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Tel: (408) 293-8881.

OB/GYN: Board Certified/Eligible—To join 30 Phys. Multispecialty Group in Central California. City of 50,000—Service area approx. 300,000. Early partnership/stockholder with **no** initial investment. Full clinic facilities 7 years old. Excellent Family/Recreational area. Contact James Simpson, MD, Visalia Medical Clinic, 5400 W. Hillsdale, Visalia, CA 93291.

OPHTHALMOLOGIST needed for 3 building medical complex located in Laguna Hills, California. Up to 2,000 sq. ft. suite with leasehold improvements. Limited partnership offers excellent tax shelter with reasonable rent. 2,500 active eye examination records offered with this exceptional opporunity. Call (714) 837-2200 days.

INTERNIST, CARDIOLOGIST, PULMONARY. No state income tax. Year round pleasant living. Equal opportunity employer. Send CV to R. J. Hudson, MD, Chief of Staff, Veterans Administration Medical Center, Marlin, TX 76661.

DOCTORS: DOCTORS: DOCTORS: International company needs doctor with own practice and office near the San Francisco financial district to undertake patients for minor cosmetic surgery. Please send résumé. All inquires confidential to Box 6211, Western Journal of Medicine, 731 Market St., San Francisco CA 94103.

CARDIOLOGIST WANTED—to associate with busy, young and aggressive cardiologist in invasive and noninvasive practice in Los Angeles. Send CV to Box 6212, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

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FAMILY PRACTICE: Washington's Cascade Mountains. Join two young board-certified FP's in challenging, comprehensive small-town practice. New clinic facility including birthing room, ER, lab, and x-ray. Outstanding hiking, skiing, fishing and scenic beauty, 85 miles east of Seattle on I-90. Contact John Anderson, MD, or Paul Schmitt, MD (509) 674-5331/201 W. Yakima Ave., Cle Elum, WA 98922.

GENERAL SURGEON—Two general surgeons in practice in Idaho are seeking a University trained associate for the practice of General, Peripheral Vascular surgery. Please send curriculum vitae to Box 6219, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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INFORMATION

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AND

(415) 777-0424

PHYSICIANS WANTED

CALIFORNIA—BE/BC. Family Physician wanted for small multi-specialty group in desirable Roseville suburb of Sacramento. Combines office practice with part-time Minor Emergency Clinic. Competitive salary. Fringe; leads to partnership. Excellent hospital and office facilities. Position available immediately. Contact Judy Cook, MD, Sierra Valley Medical Group, 1101 Smith Lane, Roseville, CA 95678, (916) 969-7767.

PSYCHIATRIST WANTED: Very active private practice in Santa Barbara need Psychiatrist. Position open in Summer or Fall of 81. Interested persons please contact Bob Hyman, MD, at (805) 964-0553.

MENTAL HEALTH PROGRAM CHIEF, SANTA BARBARA COUNTY, CALIFORNIA—Manages county-wide clinical programs and outpatient services. Requires extensive exp. in community psychiatry and desire to develop University ties. Salary DOQ. Apply to: Santa Barbara County Personnel Dept., 123 E. Anapamu, Santa Barbara, CA 93101, (805) 963-7155. Affirmative Action Employer.

ASSOCIATES WANTED

FAMILY PHYSICIAN or other primary care: To associate with long-established board certified FP. Recent ultra-modern medical office in high income area of Orange County. Major hospital close by. Community college and Calif. State Univ. in area, teaching—UCI. Write Box 6155, Western Journal of Medicine, 731 Merket St., San Francisco, CA 94103.

SITUATIONS WANTED

RADIOLOGIST BOARD CERTIFIED. Experienced in radiology and ultrasound, seeks position in Sacramento to Truckee area or available for locum tenens in August. Jack Scott, MD, 10823 Willow Valley Rd., Nevada City, CA 95959; phone (916) 265-4721.

GENERAL SURGEON University trained, Board Certified. FACS, licensed in California, Washington State, Illinois. Prefer Trauma and Critical Care management type practice. Résumé available. Reply, Box 6209, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST 34, ABIM certified, ICU fellowship, interest and training in cardiology, University trained, excellent references, prefer California coast or foothills. Box 6206, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST/ENDOCRINOLOGIST—35, board certified in both. Excellent background. Looking for practice opening in Northern California. Box 6201, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

30-YEAR-OLD ABIM certified seeks practice opportunity. Will consider group, clinic, industrial. One year private practice experience in general medicine and critical care. Write Box 6221, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER, age 36, currently in private practice in midwest, wants to move back to salt-water community on west coast (licensed California, Washington). I do general medicine, minor surgery, peds, house calls; am chairman of hospital FP/GP department and on the Preventive Medicine faculty at medical school. Have training in group therapy and emphasize patient education and comprehensive humanistic care in my practice. Looking for community, associate, or office space. Need to spend more time with family: artist/therapist wife and preschool children. Am teacher of TM technique and student of alternative healing. Box 6214, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 30)

NASA

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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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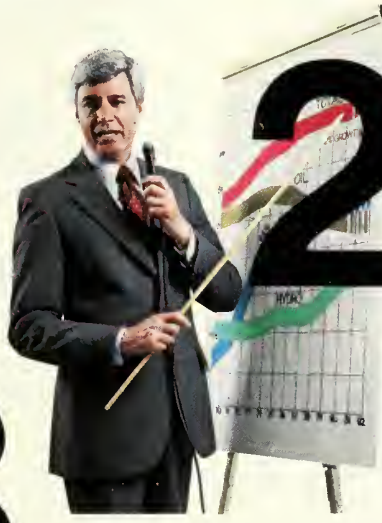
Wyeth Laboratories
Philadelphia, PA 19101

Four practical reasons to prescribe Ativan® (lorazepam) for Anxiety*

1 No interaction with more than 300 drugs†

In clinical studies, Ativan was given concomitantly with hundreds of medications, including gastrointestinal and cardiovascular, with no reported interactions. Whereas the interaction of diazepam and cimetidine has been shown to cause increased sedation in patients taking both drugs, the clearance of Ativan is not delayed by Tagamet.‡



2 Lets most patients stay active

Long-acting benzodiazepines have long-acting metabolites with activity which can produce excessive accumulation that may lead to unwanted sedation. Ativan® has no active metabolites, reaches steady state in 2 to 3 days and usually does not cause oversedation. Also, the shorter half-life of Ativan is consistent with b.i.d. dosage, so drug hangover is seldom a problem the next morning.

3 Not appreciably affected by aging

Unlike the long-acting benzodiazepines—diazepam Ⓘⓥ, chlordiazepoxide Ⓘⓥ, clorazepate Ⓘⓥ and prazepam Ⓘⓥ—the metabolism and clearance of Ativan are not appreciably affected by the aging process.

4 Not significantly affected by liver dysfunction

Ativan® is metabolized in one simple step to an inactive glucuronide; its absorption and excretion are not significantly altered by cirrhosis or hepatitis. By contrast, the metabolism of diazepam and chlordiazepoxide has been reported to be significantly altered in patients with liver dysfunction.

See important information on following page.

*Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

†All benzodiazepines, however, produce additive effects when given with CNS depressants, such as barbiturates or alcohol.

‡Tagamet (cimetidine) is a registered trademark of Smith Kline & French Laboratories, Division of SmithKline Corporation.

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Philadelphia, PA 19101

(Continued from Page 27)

SITUATIONS WANTED

MATURE GP. Experienced in minor surgery, major surgery assisting, industrial work, and general family practice. Recently closed private practice of many years. Seeking new opportunity for practice out of Los Angeles. California only. Box 6215, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FOR RURAL OR NON-METROPOLITAN HOSPITAL OR MEDICAL GROUP experienced PHYSIATRIST is available to establish or enhance Physical Medicine and Rehabilitation Dept. Competent in Orthopaedic Medicine, PM&R, including EMG's, and Sports Medicine. Box 6216, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UROLOGIST: Board certified, seeks relocation from rural environment back to suburban, urban environment. Prefer solo practice opportunity with dynamic possibilities. Write Box 6217, Western Journal of Medicine 731 Market St., San Francisco, CA 94103.

GENERAL INTERNIST, 36, ABIM certified. Seeks group position in West or Southwest. Will consider small communities. Available fall, 1981. Box 6218, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ENDOCRINOLOGIST-INTERNIST—seeks group practice opportunity in San Diego-Los Angeles area. Will consider salaried position in a hospital or a medical clinic. Reply Box 6220, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, certified (AP/CP/RIP) with special interest in Clinical Chemistry and computer applications. Also certified in Nuclear Medicine. Eight years experience in Pathology and four years experience in Nuclear Medicine. Foreign graduate, US trained, California license. Box 6213, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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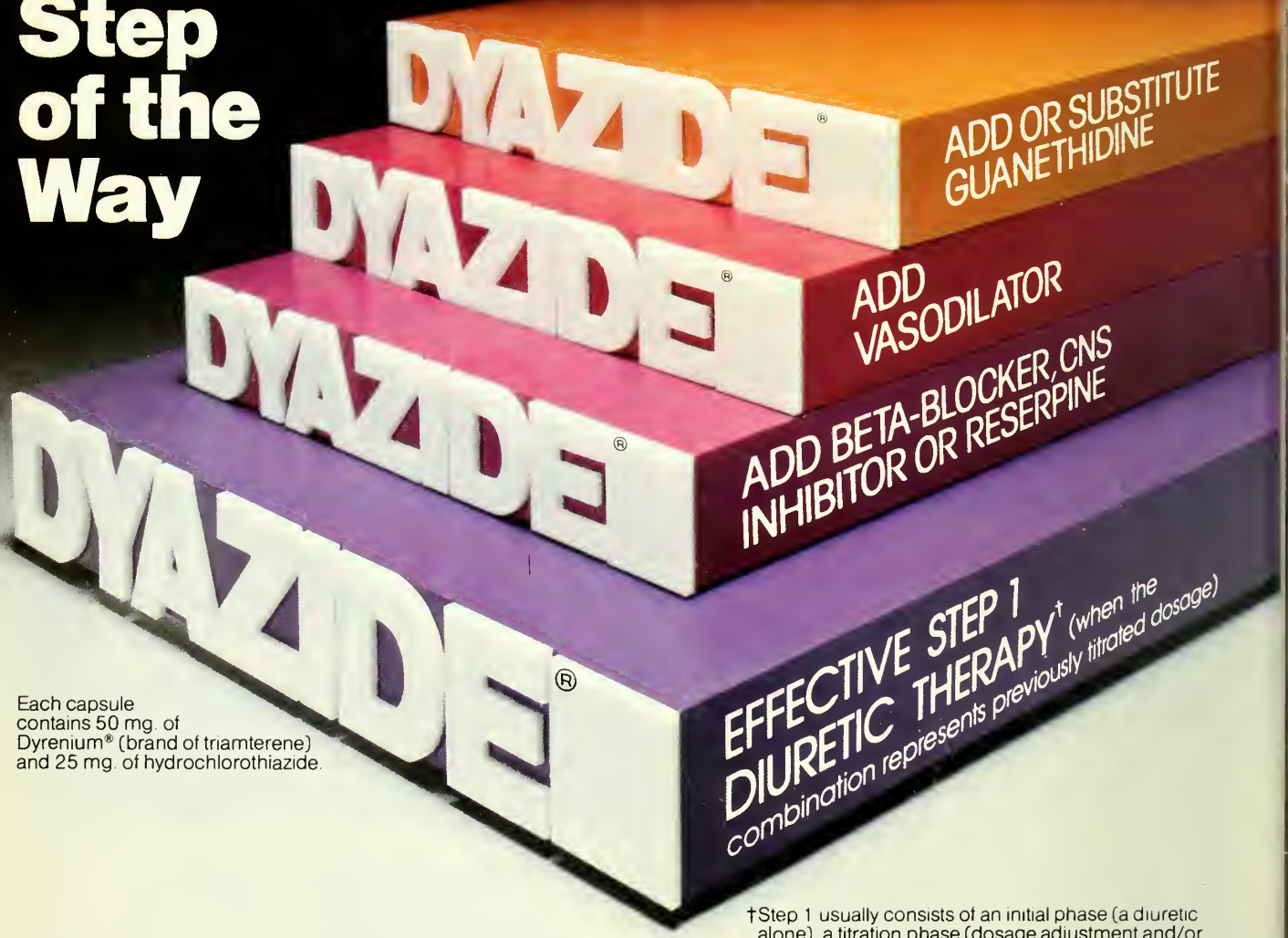

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Membranous Nephropathy: High-Dose Alternate-Day Therapy With Prednisone

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Fifteen cases were selected for study from 100 consecutive cases of membranous nephropathy diagnosed by renal biopsy and light, immunofluorescence, and electron microscopy. The cases were chosen because during a pretreatment observation period ranging from 8 to 66 months (median, 18 months), the patients' disease state had progressed. Data gathered during this period served as a baseline against which to evaluate the effects of treatment with prednisone; thus, the patients served sequentially as their own controls. All but one of the patients had nephrotic syndrome, and 11 had renal insufficiency.

Treatment with prednisone administered on alternate days was accompanied by decreasing proteinuria and increasing serum levels of albumin in all the patients. Healing, defined as proteinuria of no greater than 0.2 grams per 24 hours for at least a year with maintenance of normal creatinine clearance, occurred in eight patients. Renal function, judged by rate of creatinine clearance or level of creatinine in serum, improved in all 11 patients with renal insufficiency; in eight of these, normal function was attained. Poor renal function could not be attributed to diminished blood volume measured by chromium 51 red-blood-cell tag.

WHETHER MEMBRANOUS NEPHROPATHY responds to drug therapy of any kind remains controversial.[1-8] It has been suggested that immunosuppressive agents are worthless once renal insufficiency has occurred in this disease[9] and that renal failure in this disease usually progresses to end-stage renal failure.[1,6] Here, we present evidence that corticosteroids can reverse or arrest both the nephrotic syndrome and renal insufficiency in patients with membranous nephropathy.

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Patients, Materials and Methods

Definitions

- *The onset of membranous nephropathy:* the date of discovery of edema or massive proteinuria.
- *The nephrotic syndrome:* proteinuria of 3.5 grams or more per 24 hours with serum albumin of 3.0 grams or more per dl.
- *Normal serum creatinine levels:* 1.6 mg or more per dl.[10]
- *Normal creatinine clearance:* 72 to 141 ml

per minute per 1.73 sq meters of body surface area.[10]

- *Healed membranous nephropathy:* proteinuria less than 0.2 grams per 24 hours, maintained for at least one year, with normal renal function (defined either by normal serum creatinine levels or by normal creatinine clearance).
- *Improved nephrotic syndrome:* conversion from the nephrotic state to a nonnephrotic state (proteinuria less than 3.5 grams per 24 hours with serum albumin greater than 3.0 grams per dl).
- *Improved renal function:* decreased serum creatinine levels or increased creatinine clearance, or both.

Patients

This study was derived from the cases of 100 patients with membranous nephropathy diagnosed by renal biopsy assisted by light, immunofluorescence and electron microscopy.[11] Of the 100 patients, 68 were treated with corticosteroids according to our treatment protocol. From these 68 patients, a biased selection of 15 patients was made of those whose cases had been followed during a control period of 8 to 66 months (median 18 months), during which time their renal status was deteriorating: in 11, various degrees of renal insufficiency had developed, some severe (Table 1); 14 had nephrotic syndrome by the strict definition we have used (see *Definitions*); a 15th patient (patient 6) narrowly missed having nephrotic syndrome as defined. Clearly, the selection favored an unfavorable course[1,6,9] as shown by a sequential control period against which to evaluate the effects of treatment. The cases of the other 53 patients with membranous nephropathy treated with glucocorticoids were excluded because there had not been a period of follow-up during which renal status was deteriorating. Many of these patients did well also. Women fared better than men. The course of all 68 patients is the subject of a separate report.[11] The 32 untreated patients were not treated with corticosteroids for various reasons: refusal; mildness of the disease (for example, proteinuria less than 5 grams per 24 hours with normal creatinine clearance and normal serum albumin levels); old age; inability to tolerate test doses of prednisone (severe alteration of sensorium, for instance). Thus they were not suitable as parallel controls. The 32 untreated patients did less well than the patients treated with corticosteroids.[11]

TABLE 1.—*Clinical Data for Patients With Membranous Nephropathy Before and After Treatment With High-Dose, Alternate-Day Prednisone*

Patient	Age(Sex) at Onset of Membranous Nephropathy (yr)	Duration of Disease Before Treatment (mo)	Status of Patient Before Treatment: BP	BV/HCT (%)	Cr_s/C_{cr} (mg/dl) (ml/min)	Serum Albumin (grams/dl)	Proteinuria (grams/24 hr)	Prednisone Treatment: Maximum Dose (mg/48 hr)	Duration at Maximum Dosage (mo)	Optimal Status of Patient During or After Treatment: Months After Starting Treatment	Cr_s/C_{cr} (mg/dl) (ml/min)	Serum Albumin (grams/dl)	Proteinuria (grams/24 hr)	Status of Patient at Last Observation: Cr_s/C_{cr} (mg/dl) (ml/min)	Serum Albumin (grams/dl)	Proteinuria (grams/24 hr)	Total Follow-up Since Onset of Disease (mo)
1	32(F)	8	82	../36.0	1.0/130	1.8	6.5	100	12.0	7	0.9/ 94	4.1	<0.2	0.9/ 90	4.0	<0.2	78
2	35(F)	23	107	../38.0	1.0/ 48	2.6	10.0	200	6.0	24	0.7/ 85	4.0	1.5	0.9/ 76	4.5	<0.2	102
3	39(F)	11	93	76/43.0	0.6/...	2.1	6.3	200	14.5	15	0.9/102	4.2	<0.2	0.7/129	3.9	<0.2	86
4	36(M)	30	83	96/35.6	2.2/ 69	1.3	20.0	100	16.0	18	1.4/120	4.4	3.3	1.0/102	5.2	<0.2	224
5	43(M)	66	147	../32.0	2.4/ 45	1.7	16.5	120	4.0	15	1.6/ 86	4.5	2.5	1.4/103	4.0	2.3	157
6	65(F)	34	113	../24.0	4.1/ 26	3.4	7.5	100	3.0	9	3.2/ 40	4.3	1.0	3.1/ 43	4.8	1.5	49
7	31(M)	2	97	95/45.2	0.9/110	1.0	16.0	200	6.0	17	0.8/123	2.3	2.2				
		24*	93	../..	1.2/ 82	1.7	7.0	200	7.0	16	0.8/107	3.5	1.6	1.0/118	3.8	2.3	70
8	14(M)	17	97	90/39.0	2.0/ 50	2.5	20.0	200	7.5	24	1.2/100	4.1	1.8	2.3/ 48	3.2	14.6	166
9	37(M)	18	107	96/37.9	4.5/ 25	2.3	14.3	100	10.5	11	2.0/ 49	3.0	1.5	1.3/...	4.1	<0.2	206
10	33(M)	34	140	105/31.0	4.0/ 31	2.0	14.0	200	8.0	39	1.0/106	3.8	3.3	1.5/...	2.9	2.6	124
11	64(F)	12	100	82/37.6	1.0/ 67	2.0	9.0	200	3.0	10	0.9/ 79	3.0	0.5	0.7/120	2.6	1.1	34
12	54(F)	9	100	92/44.0	0.9/126	2.1	11.0	100	8.5	5	1.0/105	3.8	<0.2	.../...	...	<0.2	180
13	48(M)	13	107	87/51.6	2.3/ 48	2.5	12.0	100	8.5	19	1.6/ 68	4.5	1.0	2.0/ 38	4.6	0.5	161
14	56(F)	23	93	../33.0	3.0/ 23	2.0	18.7	60	13.0	30	1.9/ 48	4.0	0.9	1.1/ 76	4.6	<0.2	86
15	16(M)	8	110	80/31.4	2.6/ 36	1.0	20.0	200	7.0	17	1.4/106	4.8	<0.2	1.6/ 79	5.0	1.0	128

BP = mean blood pressure just before renal biopsy; BV = total blood volume; HCT = hematocrit of peripheral venous blood; Cr_s = serum creatinine; C_{cr} = creatinine clearance in ml/min, corrected to 1.73 M^2 body surface area.

The patients ranged in age from 14 to 65 years (median, 37 years) at the clinical onset of membranous nephropathy. Seven were women, and eight were men.

Methods

The blood and urine chemistry techniques used were those in use at the clinical laboratories of the University of California, San Francisco.

Blood volume was measured by chromium 51 red-blood-cell tag[12,13] in ten patients. The patients were in a steady state, were not taking diuretics in most cases, and had been lying down for at least an hour when the measurements were made, just before renal biopsy. Blood samples were taken without stasis. Blood volume was reported as the percentage of the normal volume for a man or woman of the patient's height and weight when in good health (before the onset of edema). This method of measuring blood volume was previously described in reports from our laboratory.[12,13] The technique used for renal biopsy and to prepare renal tissue for microscopy have been previously described.[14,15]

Treatment

The general plan was to give prednisone on alternate days in dosages of 100 to 200 mg per 48 hours for six to 12 months, with monthly decrements of 20 mg per 48 hours as soon as proteinuria decreased to 2.0 grams per day. We arrived at this relatively high corticosteroid dosage schedule through many years of trial and error. We further emphasize that in our experience not all patients respond to the same dose and duration of prednisone treatment. That is, treatment must be individually determined. The danger of a fixed dose and duration of corticosteroid treatment as used in some double-blind studies is well illustrated by the case reported in the appendix of a previously published article,[15] in which a small woman given 40 mg per day of prednisone for one year was not cured of her nephrotic syndrome. Her nephrotic syndrome was brought rapidly under control by increasing the prednisone dosage to 85 mg per day, and she was ultimately cured. However, a severe cushingoid state had developed with compression fractures of the spine as a result of the prolonged 40-mg per day dosage schedule. We now start with alternate-day administration of prednisone in a 100-mg dose. If in a month favorable effects are not occurring, we then increase prednisone dosage. We do not consider that a patient with membranous nephropathy who does not respond has had a sufficient trial until the patient has had at least a six-month course of alternate-day therapy with prednisone.

The patients' dietary regimen included sodium restriction, a high caloric intake (55 calories or more per kg of body weight per day) and a protein intake of 100 to 130 grams per day unless contraindicated by renal failure.

Supplemental potassium, antacids (aluminum hydroxide gel or calcium carbonate), tranquilizers and antituberculous medication were given as needed. Antihypertensive medication was given as needed to keep blood pressure at or below 140/90 mm of mercury. When possible, particularly during the first few weeks of prednisone therapy, we gave no diuretics, so that the effect of the therapy could be better appreciated.

Results

Clinical Data

The pertinent clinical data on the 15 patients are summarized in Table 1. Patient 7 had two courses of prednisone treatment; the first was given after a two-month observation period, and the second after a 24-month observation period, during which he again became nephrotic. In all the patients, the diagnosis of membranous nephropathy was confirmed by renal biopsy during the pretreatment observation period. At this time, serum creatinine was elevated (greater than 1.6 mg per dl) in 9 patients, and creatinine clearance was diminished (less than 72 ml per minute per 1.73 sq meter of body surface area) in 11. Blood volumes ranged from 76 to 105 percent of the predicted volumes.[12,13] No consistent relationship between blood volume and creatinine clearance was noted.

For each patient the dose of prednisone every 48 hours and the duration of treatment at this dosage in months is shown in Table 1. After the period given in the table, therapy was gradually discontinued by decreasing the alternate-day dose by 20 mg decrements each month.

Table 1 also shows the duration of clinical follow-up after the onset of membranous nephropathy. The follow-up period ranged from 34 to 224 months (median, 126 months). None of the patients had died.

Healing

Four patients (patients 1, 3, 12 and 15) healed (see *Definitions*) during the treatment, and three

(patients 2, 4 and 9) improved during the treatment and healed after it had been discontinued. Only one of the seven healed patients (patient 15) had a recurrence of proteinuria, and this proteinuria was slight (1.0 grams per 24 hours).

Although all the patients improved during prednisone therapy, patients 8 and 13 regressed with respect to creatinine clearance. In both, initially there was favorable response to further courses of prednisone but subsequently creatinine clearance decreased and proteinuria increased. These cases were followed for 166 and 161 months, respectively.

Case Results

The response of membranous nephropathy to alternate-day treatment with prednisone is shown in Figures 1 and 2 for patients 3 and 15. In one case, patient 3, observation was maintained for 11 months before treatment was begun. Her renal function remained normal throughout the observation and treatment periods. Her protein-

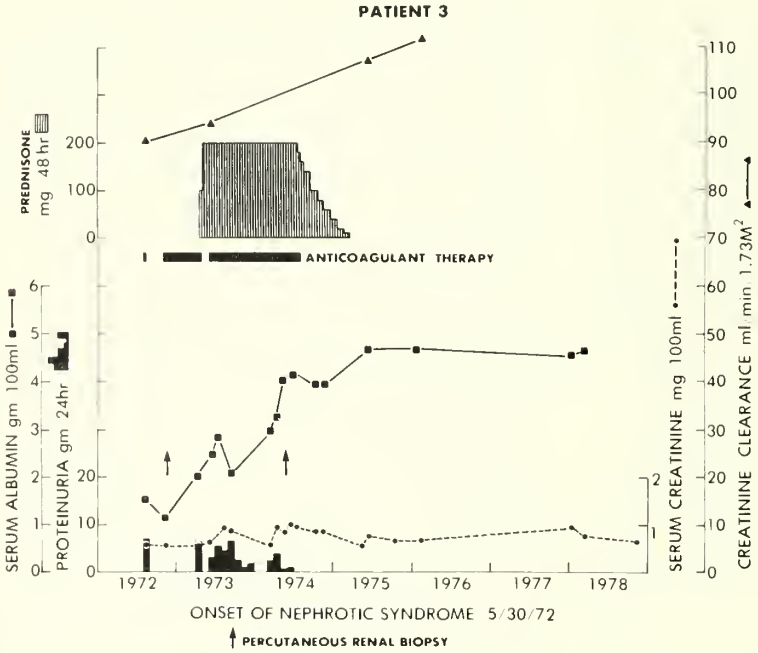

Figure 1.—Response of membranous nephropathy to alternate-day prednisone treatment in nephrotic patient, showing normal kidney function.

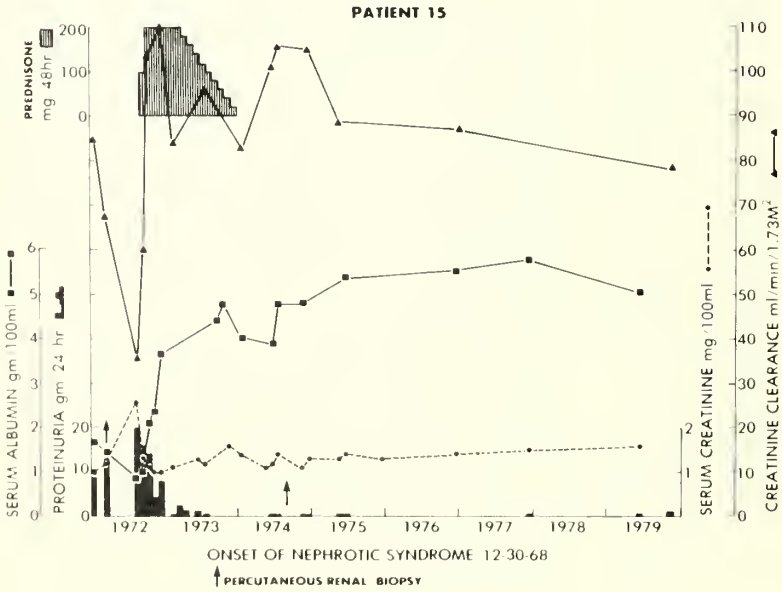

Figure 2.—Response of membranous nephropathy to alternate-day prednisone treatment in nephrotic patient with renal failure.

uria test results became negative during treatment and she remained healed. Patient 15 had declining creatinine clearance and serum albumin and had increasing proteinuria during his eight-month pretreatment observation period. When treatment was started, his serum creatinine value was 2.6 mg per dl, creatinine clearance was 36 mg per minute per 1.73 sq meters of body surface area, serum albumin was 1.0 grams per dl and proteinuria was 20.0 grams in 24 hours. During treatment his renal insufficiency, proteinuria and hypoalbuminemia rapidly improved; renal function completely returned. His urine remained protein-free for about 2½ years, but more recent tests showed proteinuria of up to 1.0 grams per 24 hours.

Improvement of Renal Function

During treatment with prednisone, the concentration of creatinine in serum diminished in all nine patients in whom it had been elevated before treatment, returning to within normal limits in all but three of the nine (patients 6, 9 and 14). In patients 9 and 14, serum creatinine levels decreased during treatment and reached normal ranges after treatment was discontinued.

Creatinine clearance increased during prednisone therapy in all 11 patients in whom it had been diminished before the therapy, attaining normal ranges in seven (Figure 3). Patient 11 continued to improve and normal clearance was attained after the treatment had been discontinued (Figure 3).

Patient 13 (previously reported as case 1[16] and case 4[17]) warrants special mention. During the pretreatment observation period, renal-vein thrombosis developed with complete thrombosis of his right kidney. In July 1966 this kidney, which was functionless, was removed, and a large thrombus was surgically removed from his inferior vena cava. He was then given anticoagulant treatment. Thus, the last data shown for him reflect the status of a single kidney. The function of this kidney did not improve while he was receiving sodium warfarin alone, but prednisone therapy was accompanied by a rise in creatinine clearance from 40 to 68 ml per minute per 1.73 sq meters of body surface area.

The patients with a normal rate of creatinine clearance before treatment fared much better than those with a diminished rate of clearance. Of the four patients with normal creatinine clearance (patients 1, 3, 7 and 12), in all but one (patient 7) there was healing of the nephrotic state, sustained at the latest observation. In contrast, the nephrotic state healed in only four (patients 2, 4, 9 and 14) of the 11 patients whose rate of creatinine clearance was diminished before treatment. The responsiveness to treatment appeared to be greater in patients with normal renal function at the beginning of treatment than in those with diminished function, but the difference was not statistically significant ($P<0.55$ by the chi-square test with continuity correction method), probably because of the small sample size.

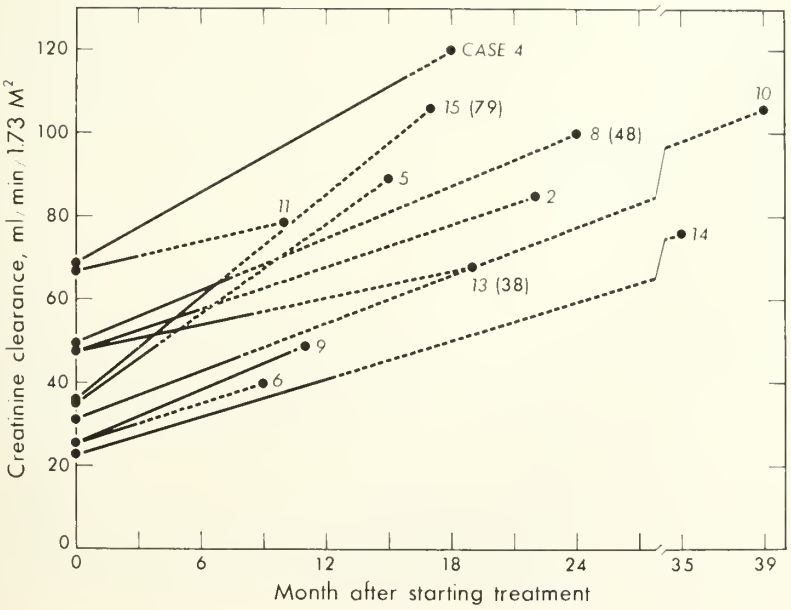

Figure 3.—Improved creatinine clearance from alternate-day prednisone treatment in 11 patients.

Complications of Prednisone Therapy in the 15 Patients

- In patient 2 a diabetic state developed which required insulin therapy and which completely subsided when prednisone therapy was stopped.
- In patient 10 aseptic necrosis of the right femoral head developed, requiring a prosthetic transplant. His left hip became necrotic during further courses of prednisone therapy but had not yet required replacement.
- A compression fracture of a vertebral body occurred in patient 14. The condition improved; she was ambulatory and had no physical limitations.
- Patient 11 became susceptible to bruising of the forearms.

All 15 patients were remarkably free of striae and a cushingoid state. Only one (patient 10) had residual consequences.

Blood Pressure

Blood pressure was elevated in only four patients. Hypertension was easily controlled with antihypertensive medication, usually diuretics. We noted no consistent relation between arterial hypertension and the course of membranous nephropathy in this group of patients. None of the patients had a vascular complication such as coronary occlusion or cerebrovascular accident.

Discussion

Our results show a more favorable outcome than others have reported in patients having nephropathy treated with prednisone. Table 2 summarizes six prospective controlled studies[3,4,6,8,11,24-29] that we reviewed. These investigations differ from the present study in several respects, including the diagnostic techniques used, the length of follow-up, and the dosage, duration and intermittency of treatment.

In several of the studies listed, conclusions concerning the effect of treatment were drawn from data on a small number of patients or on patients followed for only a short period. These criticisms are particularly apt in view of the known variability of the course of membranous nephropathy.

In six of the studies[18,21,22,24,28,29] the diagnosis of membranous nephropathy was consistently made only by light-microscopic study of renal

TABLE 2.—*Conclusions of Studies Reviewed Concerning Effect of Treatment in Membranous Nephropathy*

Black et al[18]	Prednisone not beneficial, possibly harmful and life-shortening.
Collaborative Study of the Adult Idiopathic Nephrotic Syndrome[19]	Prednisone had temporary beneficial effect on proteinuria and delayed progression of renal insufficiency.
Donadio et al[20]	Cyclophosphamide had no effect compared with placebo.
Lagrue et al[21]	Neither placebo nor azathioprine had effect, whereas chlorambucil had favorable effect.
Medical Research Council Working Party[22]	No statistically significant difference between patients given placebo and those given prednisone-azathioprine.
Western Canadian Glomerulonephritis Study Group[23]	No statistically significant difference between azathioprine-treated patients and prednisone-treated patients in either proteinuria or serum creatinine values.
Bolton et al[24]	Alternate-day treatment with prednisone accompanied by decreased proteinuria; renal function maintained.
Ehrenreich et al[25]	Treatment with corticosteroid/cyclophosphamide had beneficial effect.
Erwin et al[3]	Corticosteroid not effective.
Franklin et al[26]	Corticosteroid possibly beneficial.
Gluck et al[27]	Corticosteroid apparently effective in some cases; cyclophosphamide not effective.
Hayslett et al[4]	Corticosteroid not effective.
Hopper et al[11]	In a study of 100 patients with membranous nephropathy, alternate-day prednisone treatment of 68 patients was often accompanied by diminished proteinuria and serum creatinine with increased serum albumin and creatinine clearance. Outcome favorable in 67.5 percent of treated patients (26.5 percent healed; 41 percent improved). Untreated patients did less well.
Laver and Kincaid-Smith[28]	Prednisone delayed death.
Noel et al[29]	Outcome favorable in 38 percent of untreated patients (23 percent spontaneously healed; 14.6 percent spontaneously improved).
Pierides et al[6]	No difference between untreated patients and prednisone-treated patients.
Row et al[8]	No conclusion concerning effect of corticosteroid.

tissue. We have suggested,[15] as have many other investigators, that light microscopy alone is not always a reliable means of diagnosing membranous nephropathy. Accordingly, in the above six studies, some of the diagnoses could have produced misleading conclusions concerning both the natural history of the disease and the effectiveness of treatment.

Precise information on the dosage and duration of the treatment is given in only a few of the studies. Although prolonged courses of prednisone therapy were used in some, the courses were usually shorter, or the doses smaller, than those we have routinely employed.

Alternate-day administration of prednisone was reported to be beneficial in treating membranous nephropathy in three studies.[11,19,24] Only one of these[19] included a nontreated, matched control group of patients with the disease. The relapse rate of membranous nephropathy in that study was higher than that reported here, perhaps because of the short treatment period (two months). Nonetheless, the patients who received high doses of prednisone (100 to 150 mg in 48 hours) had significantly diminished proteinuria and better preserved renal function than did those who were not treated. However, the reduction of proteinuria did not persist, and the final result in the treated patients was considered to be no different than that in the control group.

Lagrue and associates[21] have shown that chlorambucil is beneficial in treating membranous nephropathy. Various other drugs, including azathioprine[21] and cylophosphamide[20] (unpublished data, Roger A. Lieberman and James Hopper, Jr.), have been found to be ineffective in treating this disease.

Corticosteroid therapy has been reported to be of benefit in some cases of membranous nephropathy in three retrospective studies.[11,24,25] We compared results of these studies and the present study with those of Noel and co-workers.[29] They used no corticosteroid or other specific treatment in 116 patients with membranous nephropathy and found that in 38 percent there was a favorable outcome (23.4 percent healed spontaneously and 14.6 percent improved). Of their 116 patients, 29 were under the age of 21 years; younger persons with membranous nephropathy are known to heal more readily than older ones.[30] Of their patients, in 19 percent renal insufficiency developed and in 43 percent there was no change; because 75.8 percent had the nephrotic syndrome at the onset of membranous nephropathy, many of those in whom there was no change probably continued to have the nephrotic syndrome. Of those in whom renal failure developed, 50 percent died. The mean period of follow-up was only 54 months; the mean age at the onset of membranous nephropathy, defined as the date of discovery of proteinuria or edema, was 37.6 years. In our 15 patients, the median age at the onset of membranous nephropathy (using the same definition as Noel and co-workers) was 37 years, and the mean period of follow-up was 126 months.

For the treated patients in the retrospective study by Ehrenreich and associates,[15] the mean age at the onset of membranous nephropathy was 44.7 years and the mean period of follow-up was 78 months. The outcome was favorable in 44.0 percent of the treated patients (23.7 percent healed and 20.3 percent improved). The incidence of death from renal failure was high (38.6 percent) in the nontreated group.

In the study by Bolton and associates,[24] all 24 patients received alternate-day prednisone treatment; the mean period of follow-up was 58 months, and the mean age at the onset of membranous nephropathy was 38.7 years. The outcome was favorable in 62.4 percent of the patients (8.3 percent healed and 54.1 percent improved). In both the Bolton and the Noel studies, immunofluorescent and electron microscopy were not used uniformly in confirming the diagnosis of membranous nephropathy.

In our previous study,[11] 26.5 percent of the corticosteroid-treated patients healed according to our criteria (see *Definitions*), and 41 percent improved, giving a favorable outcome in 67.5 percent. The mean period of follow-up, 85.6 months, was longer than in any other published study.

We conclude from the findings of the present study, our previous study,[11] the study by Bolton and associates,[24] the study by Ehrenreich and co-workers[25] and the Coggins Collaborative Study[19] that patients with membranous nephropathy fare better when treated with corticosteroids than when not treated, as in the study by Noel and associates.[29]

Improvement of Renal Function

Perhaps the most striking feature in our 15 patients was the improvement of renal function, which occurred in 11 cases (Figure 3). Black and co-workers[18] and Ehrenreich and associates[25]

have also reported improvement of renal function in patients treated with corticosteroids. The Coggins Collaborative Study[19] showed that corticosteroid therapy delays the deterioration of renal function. All patients in the Coggins study had relatively high creatinine clearances on entry into the study. Bolton and associates[24] indicated that prednisone stabilizes renal function. The improvement of renal function in our study is especially noteworthy since moderate renal insufficiency in membranous nephropathy has been reported to progress slowly but steadily to end-stage renal failure over a period of three to five years.[6,7] Cameron[1,9] stated that steroids do not favorably affect the nephrotic syndrome in membranous nephropathy and that death due to renal failure occurs when the nephrotic syndrome persists. In the study by Noel and associates,[29] renal failure occurred in 19 percent of the untreated patients in a fairly short follow-up period (mean, 54 months), and half of these patients died. No deaths due to renal failure occurred among our 15 patients.

Blood volume was measured in 19 patients, six with renal insufficiency, in order to determine whether changes wrought by the nephrotic state influenced renal function, measured by creatinine clearance. Blood volume tends to diminish in the nephrotic state and, if sufficiently low, could theoretically induce prerenal failure. Generally, blood volumes and levels of serum creatinine had no consistent relationship. Patients 10 and 11 had the highest levels of serum creatinine but were not deficient in blood volume. Accordingly, the high levels of serum creatinine and low rates of clearance in patients in whom blood volume was measured cannot be attributed to volume depletion.

Conclusion

The results of the present study suggest that high-dose alternate-day prednisone therapy is beneficial in some patients with membranous nephropathy, including those with renal insufficiency. Accordingly, we favor a trial of corticosteroid therapy in patients with membranous nephropathy who have a nephrotic syndrome, even if they have renal insufficiency. Complications of this treatment were infrequent, and relapse into nephrotic syndrome was rare.

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Pulmonary Embolism in Patients With Acute Leukemia and Severe Thrombocytopenia

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While pulmonary thromboembolism has been reported in patients with acute leukemia complicated by severe thrombocytopenia, it has been studied infrequently and its pathogenesis remains imprecisely understood. Findings of 80 consecutive autopsies of patients with acute leukemia showed that three had pulmonary thromboembolism. All three patients had been severely thrombocytopenic and had received numerous platelet transfusions. Serial sections of thrombi were evaluated with electron microscopy. In no instance were platelet aggregates detected. However, Candida *organisms were prominent in thrombotic specimens from each patient. These findings suggest that thromboembolism in such patients may involve occult fungal infection. Because pulmonary thromboembolism can complicate the course of acute leukemia and severe thrombocytopenia, it should be considered when clinical data suggest its occurrence.*

DESPITE IMPORTANT ADVANCES in the treatment of patients with acute leukemia, morbidity and mortality complicating remission induction remain high. While infection and bleeding represent the major problems, a broad spectrum of other medical and surgical complications can develop as well.[1-3] Although pulmonary thromboembolism develops less frequently in patients with leukemia than in other patients in hospital, its occurrence[4,5] can be catastrophic. Because severe thrombocytopenia often complicates acute leukemia and its treatment, it is reasonable to assume that these patients might be protected from thromboembolism, which, in turn, might account for its low incidence in this population. We report our experience with pulmonary thromboembolism in three patients with acute leukemia and provide ultrastructural details of the thrombi.

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Patients and Methods

The records of all 80 patients who died with acute leukemia at the University of Iowa Hospitals between January 1972 and December 1977 and

had autopsies were evaluated retrospectively to assess the frequency of pulmonary embolus or infarction, or both. Material indicating pulmonary infarction with no thrombosis, hemorrhagic infarction or infarction secondary to leukemic thrombi and aggregates was excluded. Cases in which thromboemboli were detected were subjected to detailed pathological reevaluation of the lung tissue and thrombi with light and transmission electron microscopy.

Complete autopsy specimens had been processed in accordance with standard procedures. These included two- to three-day fixation in 10 percent formalin buffered with 2 percent sodium acetate, progressive dehydrations with graded alcohol solutions through 100 percent alcohol, two xylene incubations and subsequent paraffin impregnation. Specimens were cut on standard microtomes and stained with hematoxylin-eosin, periodic acid Schiff, Giemsa and other specialized stains.

Areas of light microscopy specimens identified specifically as pulmonary thromboemboli were located on the intact paraffin blocks. These emboli were excised from the block and reprocessed for transmission electron microscopy. Specimens were cut into small sections and rehydrated as follows: Tissue was placed in xylene for 48 hours with frequent changes of the xylene to remove impregnated paraffin. The specimens were then rehydrated with reverse progression of graded alcohols from 100 percent to 35 percent in ½ hour incubation steps. Final rehydration was achieved with a 1½-hour distilled water incubation. Specimens were postfixed in osmium tetroxide for an hour and dehydrated in 15-minute incubations in graded alcohol solutions through 100 percent. The specimens were embedded in resin (Epon-Araldite) and sections were cut on a Reichert ultramicrotome. All specimens were examined in a Philips EM 300 electron microscrope.

Results

Three of 80 patients had pulmonary thromboemboli with infarction of the corresponding pulmonary segment (Table 1). In no case was thromboembolism in the absence of infarction noted. In each case, the gross examination suggested a recent single thromboembolus of the main pulmonary artery or one of its major branches. On histological examination, numerous emboli of the corresponding, distal small arteries were seen in each case. It was not possible to ascertain whether the lesion of the large vessel was a thrombus or embolus. The pulmonary thromboembolism was the only thrombosis observed in our patients. In particular, detailed examination of all major deep veins of the lower extremities and cardiac valves showed them free of disease that might have given rise to embolization. Histological examination of other visceral vessels was not consistent with the possibility of disseminated intravascular coagulation.

Of interest was the finding that all three of

TABLE 1.—*Clinical Features of Patients With Acute Leukemia and Pulmonary Thromboembolism*

					Initial		*Preterminal*						
Patient	*Age*	*Sex*	*Diagnosis*	*Drugs*	*Leukocyte Count*	*Platelets*	*Leukocyte Count*	*Platelets*	*Coagulation*	*No. of Platelet Transfusions/Post-transfusion Increment*	*Signs and Symptoms of PE*	*Interval from Admission to Symptoms of PE (Days)*	*Interval from Admission to Death (Days)*
1	63	F	ALL L-2	OAP	4.1	1	.5	38	PT 14 PTT 37 Fib 400	13/6-10	acute SOB tachypnea infiltrate ↓ partial pressure of oxygen	13	15
2	77	M	AUL L-1	OAP	33.8	71	.6	7	PT 11 PTT 34 Fib 355	9/0	infiltrate tachypnea tachycardia	18	21
3	63	M	AML M-1	TADPO	1.4	85	.6	2	PT 14 PTT 50 FM < 4 FDP >10 <40 Fib 640	13/0	dyspnea tachypnea infiltrate effusion hemoptysis	17	18

ALL = acute lymphocytic leukemia; AML = acute myelocytic leukemia; AUL = acute undifferentiated leukemia; FDP = fibrin degradation products; Fib = fibrinogen; FM = fibrin monomer; OAP = vincristine, cytosine arabinoside and prednisone; PE = pulmonary embolism; PT = prothrombin time; PTT = partial thromboplastin time; SOB = shortness of breath; TADPO = 6 thioguanine, cytosine arabinoside, daunomycin, prednisone and vincristine.

our patients had occult fungal infections. In each, *Candida* organisms were detected on postmortem cultures and by histological examination of the lungs. Other organs were free of fungal infection. The postmortem culture of patient 3 grew *Aspergillus* species. This organism had not been detected in any of the three patients before death, although frequent cultures had been done.

Serial sections and detailed examinations of specimens from the three patients with thromboemboli showed no platelet aggregates within any aspect of the fibrin-erythrocyte masses. However, *Candida* forms were abundant in all three. In patient 2, pseudohyphal forms of *Candida* were observed as well (Figure 1). The thrombi from patients 2 and 3 also displayed variable numbers of septate hyphal forms consistent with aspergillosis or mucormycosis. It is of note that in no case was vessel wall invasion or necrosis observed despite examination with special fungal stains (Figure 2). Likewise, fungus was not shown to be present in pulmonary vessels in segments of the lung not involved with thromboembolism.

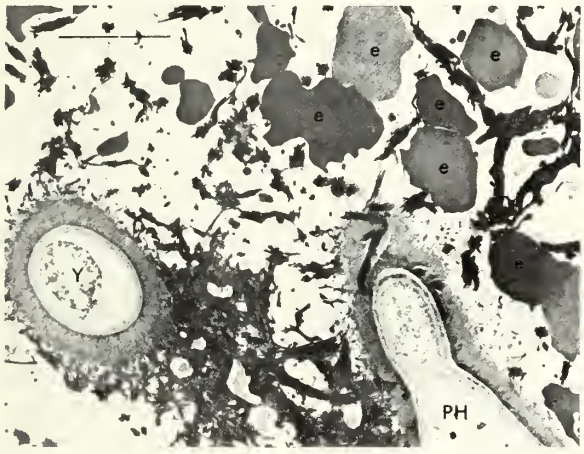

Figure 1.—Transmission electron photomicrograph of pulmonary embolus from patient 2. *Candida* organisms appear in both yeast and pseudohyphal forms (Y, PH). Fibrin enmeshes the fungal forms and surrounding erythrocytes (e). (Standard = 5 μ; lead and uranyl acetate stain, reduced from magnification ×7,000.)

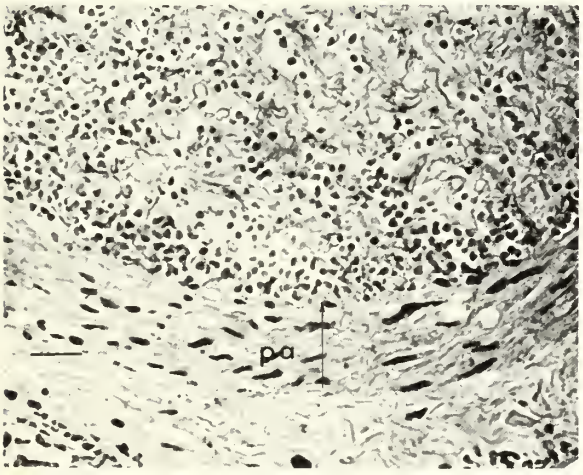

Figure 2.—Light photomicrograph of pulmonary artery (pa) and embolus from patient 3. The intimal surface of the artery **(arrow)** surrounds the body of the fibrin-erythrocyte embolus. (Standard = 50 μ; hematoxylin-eosin stain, reduced from magnification ×250.)

One patient was thought to have acute myelocytic leukemia, one had acute undifferentiated leukemia and one was found to have acute lymphocytic leukemia. All were severely pancytopenic as a result of chemotherapy, and each had received numerous platelet transfusions. In patient 1, there was progressive refractoriness to transfusion, in that the platelet count after transfusion rose only modestly. In patients 2 and 3 there was no rise.

In retrospect, in all three patients signs or symptoms consistent with, but not specific for, pulmonary embolism had developed. These are summarized in Table 1. A pulmonary infiltrate, corresponding to the location of the thromboembolism was noted in each. Acute, episodic dyspnea, tachypnea, hypoxemia and hemoptysis were commonly observed. Pleuritic chest pain was not noted. The coagulation data as well as results of peripheral smear examinations suggest that disseminated intravascular coagulation (DIC) or microangiopathic hemolytic anemia were unlikely causes of thrombosis. Other factors which might have predisposed these patients to thromboembolism, such as trauma of a lower extremity, a recent operation or dehydration, were absent; however, all three patients had been bedridden and inactive.

Discussion

The incidence of pulmonary thromboembolism at autopsy in patients with acute leukemia was reported as less than 1 percent by Boggs and coworkers[5] and 6.3 percent by Wiernik and Serpick.[4] The incidence in our study was 3.8 percent (3 of 80). However, the significance of this problem may be greater given the number of patients surviving induction. Generally, in patients with leukemia and severe thrombocytopenia, it is not considered likely that pulmonary thromboembolism will develop. Thus, the diagnosis is not pursued or established before death in such patients. It seems reasonable on the basis of autopsy data, however, to say that the incidence of pulmonary thromboembolism is indeed lower in these pa-

tients than in other patients in hospital. Incidence in the latter is reported to be between 14 percent and 68 percent, depending on autopsy techniques applied and patient selection.[6-8]

The mechanism of thromboembolism in such patients is of interest. While the role of platelets in venous thromboembolism is not completely understood, evidence suggests that it may be important in patients with normal platelet counts.[9] It is not surprising, therefore, that severe thrombocytopenia should afford some degree of protection against thrombosis. That this protection is not complete is suggested by findings from studies in animals which showed thrombosis in the absence of platelets,[10,11] and by our own clinical observations.

Stasis of venous flow, generally from inactivity but also from mechanical factors, is a potent risk factor for venous thrombosis.[12] Our patients were clearly desperately ill and inactive. However, the absence of thrombosis in the lower extremities mitigates against this factor, although it is conceivable that the lower extremity thrombosis may completely embolize, autolyze or be overlooked if careful examination is not done.[13]

Malignant cells, including leukemic myeloblasts, have been noted to elaborate procoagulants,[14,15] as well as other substances, which have been felt to play a role in the occurrence of disseminated intravascular coagulation, which frequently occurs in leukemic patients especially during cytolytic therapy. The coagulation data and findings of histological examination of the three patients from our institution are not consistent with the features of DIC. Moreover, the time course would be atypical for this mechanism in that thrombosis seemed to occur well after nadir had begun, when the tumor burden was presumably low and cell death has passed.

Chemotherapy could conceivably cause thrombosis by direct damage to the vascular endothelium. Alternatively, the neutropenia common to all three patients could predispose to thrombosis in that neutrophils are a potential source of anticoagulant material[16] and fibrinolytic activity.[17] Whether these in vitro observations have relevance to clinical thrombosis remains to be shown.

Platelet transfusions have become a mainstay of supportive care for patients with acute leukemia. In those in whom there are good responses to transfusion, it is conceivable that improvement of platelet counts would restore hemostasis to a more normal state and, thus, remove the "protective" antithrombotic effect of thrombocytopenia. However, all of our patients undergoing induction therapy received numerous platelet transfusions, and during the latter stages of their treatment, showed poor increments in platelet counts following transfusion. Because aggregating antibodies develop to platelets from unmatched donors, platelets transfused to such patients could result in platelet aggregates and provide a nidus for thrombosis. The absence of platelet aggregates from the thrombi of our three patients suggests that there is no active role for the platelet aggregate in initiating thrombosis. Alternatively, however, aggregating transfused platelets might incite thrombosis by making platelet procoagulant substances available. This or another humoral mechanism like it would be consistent with the absence of platelets noted in our ultrastructural examinations.

The prominence of candidal and fungal forms in the composition of the thrombi of the three patients from our institution seems too abundant to be accounted for by passive absorption. The postmortem association between invasive fungal infection and thrombosis has been described for candidiasis,[18] mucormycosis[19] and aspergillosis.[20] In many of these cases, the patients suffered neoplastic diseases and were receiving myelosuppressive therapy which caused severe thrombocytopenia. Also, in some instances signs and symptoms mimicking pulmonary embolus were observed. The thrombogenic capacity of the fungal organisms may be related to their ability to secrete lytic enzymes and invade vessel walls and tissue parenchyma, thus making thromboplastins available.[18] However, the absence of vascular invasion in our sections even on fungal stains, mitigates against this. Evidence has been found of a cell-bound procoagulant produced by various fungi in an in vitro platelet-free system,[21] and, conceivably, it may place patients infected with these organisms at greater risk for thrombosis. However, in our laboratory, we have found no procoagulants produced by a variety of fungi (M. N. Stein, unpublished observations, September 1978). While *Aspergillus* has been shown not to elaborate thromboplastin, it can initiate thrombosis by shearing erythrocytes on its hyphae, producing microangiopathic hemolytic anemia, with release of erythrocyte procoagulants associated with membrane phospholipids.[22] While a series of three patients is too small to allow a statistical comparison, the fact that all patients with leukemia and pulmonary thromboembolism had occult fungal in-

fection appears to reflect an incidence higher than that of fungal infection at autopsy for patients with leukemia but without pulmonary thromboembolism during the same period at our hospital (25 of 77 or 33 percent). However, the possibility remains that the association is not causally related, but perhaps due to trapping of the organisms by an organizing thrombus which was initiated by other events. Further studies are needed to clarify the role of fungal infections in the development of pulmonary thromboembolism in such patients.

Conclusion

Pulmonary embolism infrequently complicates the course of patients with acute leukemia and severe thrombocytopenia. A higher index of suspicion may lead to the diagnosis, but the signs and symptoms are variable and nonspecific as with pulmonary embolism in other populations. The cause remains unclear but may involve occult fungal infection as well as other factors.

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Benefits of a Sleep Disorders Clinic in a Veterans Administration Medical Center

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The Sleep Disorders Clinic at the San Diego Veterans Administration Medical Center provides a diagnostic service within a public hospital. Case records of the first 117 patients receiving polysomnograms in our clinic were reviewed. Of these patients, 44 percent were found to have sleep apnea, 24 percent nocturnal myoclonus and 8 percent narcolepsy. Our experience shows that in a health maintenance organization, a sleep disorders clinic provides diagnostic information (based on a polysomnogram and a sleep history) which is very helpful in the final diagnosis of medical disorders. Very few recordings were noncontributory. In this setting, a sleep disorders clinic is justified by its rich diagnostic yield.

INCREASING NUMBERS of sleep disorders clinics are being founded as diagnostic polysomnography (sleep laboratory recording) has become a recognized clinical tool. As exemplified by members of the Association of Sleep Disorders Centers, most clinics are supported by service fees. Doubt has been raised whether polysomnography can be justified as part of accepted clinical practice.[1] The issues are in many ways similar to those posed by computed tomography—another new technical procedure which has had a notable impact on contemporary medical economics.[2]

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The potential value of polysomnography may best be evaluated in a health maintenance organization where the incentives favor limiting referrals and the number of polysomnograms done to obtain the maximum benefit from limited resources. Our Sleep Disorders Clinic is unusual in that it is not supported by service fees but receives its funding from the clinical budget of the Veterans Administration Medical Center (VAMC), in San Diego, California.

The most common complaint of patients seen at a sleep disorders clinic is insomnia, although excessive daytime somnolence is common as well. Between 10 percent and 40 percent of the population report troubles with sleep, depending on how questionnaires are phrased.[3] Recently, it has been recognized that specific physiological sleep disorders may be serious. Many of the people complaining of insomnia or of excessive fatigue

have a specific sleep disorder, such as sleep apnea, narcolepsy or nocturnal myoclonus.

Sleep apnea is a repetitive process of respiratory cessation during sleep. The sleep apnea syndrome encompasses three disorders. Obstructive sleep apnea usually involves collapse of the pharyngeal airway with partial or complete blockage of airflow. Central sleep apnea results from failure of the respiratory neurons to activate the phrenic and intercostal motor neurons that mediate respiratory movements. Mixed sleep apnea is a combination of obstructive and central apnea.[4] Apneic episodes last from 10 to 180 seconds and may occur as often as 500 to 600 times each night. Most episodes of apnea are terminated by transient arousals. In addition, episodes of hypoventilation (caused by either obstruction or by central mechanisms) may produce anoxia or arousal even when complete apnea does not occur.

Narcolepsy is characterized by sudden sleep attacks and cataplexy (sudden weakness or paralysis).[5] Persons with narcolepsy also often complain of hypnagogic hallucinations, sleep paralysis while falling asleep, automatic behaviors and disrupted nocturnal sleep.

In nocturnal myoclonus, periodic leg jerks or muscle twitches occur every 20 to 40 seconds during parts of the night. As in sleep apnea, the leg jerks are often followed by transient arousals, and, subjectively, the patient may experience both disruptions of sleep and daytime fatigue or somnolence.[6]

Only a complete sleep history and laboratory polysomnogram can help a clinician make a diagnosis and distinguish one disorder from another. To obtain maximal health benefits from limited resources, our clinic focused on patients whose complaints raised suspicion of the presence of these three specific sleep disorders.

Method

Case records of the first 170 patients contacting the Sleep Disorders Clinic were examined. Most were either self-referred or referred by one of the medical services within our VAMC, although some veterans were referred by private physicians. All patients were interviewed first. No polysomnograms were recorded for 53 patients because no recording seemed necessary after our history had been obtained, the referring physician did not desire such follow-up data or the the patient failed to keep his appointment. Data on the 117 patients who received diagnostic polysomnography are reviewed below.

TABLE 1.—*Diagnoses of 117 Patients*

Diagnosis	*No. of Patients With Presenting Complaints**			*Total Number(%)*
	DOES(%)	*DIMS(%)*	*MISC(%)*	
Sleep apnea ...	32	12	7	51(44)
Nocturnal myoclonus (without other sleep disorders)	5	6	1	12(10)
Narcolepsy	7	..	1	8(7)
Other†	11	26	9	46(39)
TOTAL	55(47)	44(38)	18(15)	117(100)

*DIMS = Disorders where difficulty initiating or maintaining sleep was the chief complaint. DOES = Disorders where excessive somnolence was the chief complaint. MISC = Miscellaneous complaints: shortness of breath or apnea (N = 6), nightmares (N = 2), falling (N = 2), depression (N = 2), leg jerks (N = 1), paralysis at sleep onset (N = 1), blackouts (N = 1), disorientation (N = 1), snoring (N = 1) and loss of erection (N = 1).

†Other diagnoses: Unknown cause (N = 12); without objective findings (N = 2); hysteria/neurosis (N = 2); organic brain disease (N = 2); Kleine-Levin syndrome (N = 1); circadian rhythm disturbance (N = 1); sleep disturbance secondary to drugs (N = 9), secondary to depression (N = 11), secondary to drugs and depression (N = 2), secondary to anxiety (N = 2), secondary to schizophrenia (N = 1) and secondary to alcohol abuse (N = 1).

Each of the 117 patients was recorded for at least one full night (N = 107) or one diagnostic afternoon nap (N = 10). During each recording, an electroencephalogram, electro-oculogram, chin electromyogram, electrocardiogram, tibialis electromyogram and respiration were monitored using standard methods. In selected cases, additional measures such as esophageal balloon pressure, pharyngeal carbon dioxide concentration and arterial oxygen were recorded.

A diagnosis of sleep apnea was based on a patient's sleep history, the number of apneic episodes (30 or more, each longer than 10 seconds), and the extent of sleep disruption detected in the polysomnograms. A diagnosis of nocturnal myoclonus was based on history and the number of disruptions of polysomnographic sleep caused by leg jerks. Narcolepsy was diagnosed based on a sleep history (especially cataplexy), REM (rapid eye movement) periods at the onset of sleep and, often, by the results of a multiple sleep latency test.[7]

Results

The patients ranged in age from 20 to 82 years (median age 52 years); 28 (23 percent) were

TABLE 2.—*Characteristics of Sleep Apnea*

Chief Compliants	*No. of Patients*	*Percent*
Excessive somnolence	32	62
Insomnia	12	24
Shortness of breath/"apnea"	5	10
Falling sensation	1	2
Excessive snoring	1	2
TOTAL	51	100
Other Symptoms		
Obesity	28	55
Snoring*	26	51
Hypertension	16	31
Shortness of breath	6	12
Depression	4	8

*Although 26 patients with sleep apnea had documentation of snoring in the medical charts, there were those where there were no bed partners to confirm or deny the snoring. We have found a higher incidence of snoring by history (79 percent) in obstructive sleep apnea patients when bed partners or medical personnel could be interviewed.

younger than 40 years, 29 (25 percent) were between 40 and 49 years, 37 (32 percent) were between 50 and 59 years and 23 (20 percent) were older than 60 years. Of the 117 patients, 108 were men, reflecting the veteran population.

Table 1 shows the relationship of the presenting complaints with the diagnoses made at the Sleep Disorders Clinic. Almost half the patients complained of excessive somnolence. The others complained of difficulty initiating or maintaining sleep or other miscellaneous problems. Of all the patients, 44 percent had some form of sleep apnea and 24 percent had nocturnal myoclonus, sometimes accompanying other conditions.

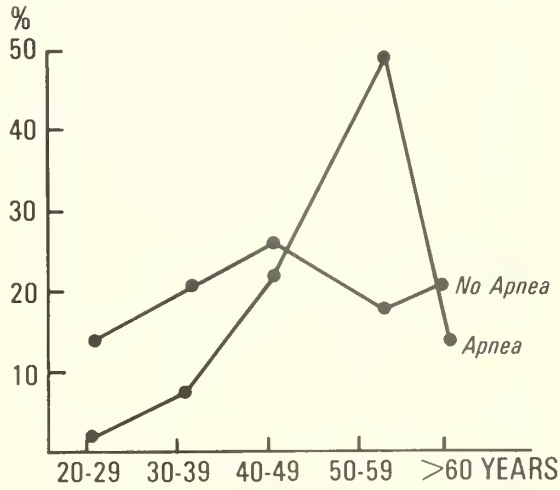

Figure 1.—Age distribution of patients with sleep apnea compared with patients without sleep apnea ($P < 0.05$).

Patients With Sleep Apnea

Of the 117 patients recorded, 51 had sleep apnea. Of these, 27 (53 percent) had obstructive sleep apnea; 10 (20 percent) had both obstructive sleep apnea and nocturnal myoclonus, 3 (6 percent) had central sleep apnea, 1 (2 percent) had central sleep apnea and narcolepsy, 1 (2 percent) had central sleep apnea and nocturnal myoclonus, 5 (10 percent) had mixed (central and obstructive) sleep apnea, 3 (6 percent) had mixed sleep apnea and nocturnal myoclonus, and 1 (2 percent) had mixed sleep apnea, nocturnal myoclonus and narcolepsy.

The chief complaints and symptoms of the 51 patients with sleep apnea are summarized in Table 2.

The age distribution of the patients with apnea was compared with that of patients without apnea. The mean age of those with apnea was 51.6 years while the mean age of those without it was 41.5 years (chi square = 16.93; $P < 0.05$; see Figure 1).

Nine patients (three with mixed sleep apnea and six with obstructive sleep apnea) were treated by tracheostomy. In eight of the nine, the symptoms largely remitted after the operation, and these patients are doing well. The ninth, in whom mixed sleep apnea was complicated by narcolepsy, gained little benefit, and the tracheostomy was allowed to close.[8]

Eight obese patients were admitted to the metabolic unit at the VAMC and were treated by a dietary regimen. Thus far, four of these have reduced their weights to within normal limits. For three of these patients, weight loss resulted in a reduced number of apneic episodes, reduced hypertension and lessened somnolence. The fourth patient still complains of somnolence and the number of apneas did not diminish after weight loss; a tracheostomy is being considered.

Two patients have been treated with imipramine. Both have improved and are doing well.

Five patients with apnea died. In each case, either the referring physicians or the patient had decided against specific treatment because of other complicating medical problems. One died suddenly in his sleep at age 47, probably from apnea. Another died suddenly in sleep but was known to suffer cardiac and renal failure. The third died at age 56, a year after apnea had been diagnosed. The cause of death was cardiorespiratory failure, possibly due to obesity. A fourth died of Hodgkin's disease at age 62, four months after obstruc-

tive apnea was diagnosed. The last patient died at age 61, two years after apnea was diagnosed. The cause of death was pneumonia.

Unfortunately, 27 patients were lost to follow-up after diagnoses and referrals were made.

Patients With Nocturnal Myoclonus

Of the 117 patients, 12 (10 percent) had uncomplicated nocturnal myoclonus. Six of these had difficulties initiating and maintaining sleep, five had disorders of excessive somnolence, and one complained of having restless legs during sleep. Three also snored, and three had depressive symptoms as well. Fifteen other patients had nocturnal myoclonus complicating sleep apnea, and one had nocturnal myoclonus in addition to narcolepsy. Combined diagnoses were made only if leg jerks were recorded at times when there were no apneic episodes.

Of the 12 patients with uncomplicated nocturnal myoclonus, 2 are receiving diazepam with symptomatic benefit. The patient with narcolepsy and nocturnal myoclonus is being treated with methylphenidate and imipramine, and both his somnolence and cataplexy are under control. Ten patients have been lost to follow-up.

Patients With Other Conditions

Based on history and polysomnograms, specific diagnoses of sleep disorders related to depression (N=13), drug and alcohol abuse (N=10), organic brain disease (N=2) and factitious complaints (N=4) were made. In some cases, these diagnoses could not have been made without data from the sleep recordings to disprove or confirm the sleep complaint.

In the cases of several additional patients, even when no new or unique diagnosis was made, the polysomnograms proved useful in documenting that an objective sleep disorder existed. For example, one patient's complaint that his back pain allowed him less than an hour's sleep nightly was documented. Such documentation also had medicolegal value or permitted staff to refuse drugs of abuse to demanding patients. Only rarely was a polysomnogram noncontributory.

Discussion

In a health maintenance organization, a sleep disorders clinic tends to discourage unnecessary referrals and limit polysomnography to those patients for whom a clinical indication is strong. In such a setting, we found that polysomnography resulted in specific diagnoses in 90 percent of the patients recorded. Of these, 43 percent had sleep apnea and 61 percent had either sleep apnea, nocturnal myoclonus or narcolepsy. Thus, in most of our cases, the Sleep Disorders Clinic contributed to the diagnosis of a specific physiological disorder.

Polysomnograms frequently led to specific medical treatments. For example, nine patients received tracheostomies in our center (some also had operations elsewhere), eight received recommendations for weight reduction and many received recommendations for taking specific medications. Several patients, particularly those with sleep apnea or narcolepsy, were relieved of partial or total occupational disabilities by specific treatments. At least seven patients who had been totally disabled were enabled to return to full-time work. At present, we cannot determine if therapy based on the Sleep Disorders Clinic examinations has resulted in prolonging life, but we are impressed that none of the patients who have followed our treatment recommendations (involving tracheostomy, weight loss, drugs and so forth) have yet died, whereas five patients with sleep apnea who did not receive specific treatments have died. Admittedly, several of the patients who died were already too ill to make treatments such as tracheostomy promising.

In addition, since the end of this survey, two additional patients have received tracheostomies, and both of them have shown improvement. Three other patients with sleep apnea underwent a successful weight reduction program. In these more recent cases, drastic improvements in reducing daytime somnolence occurred with only a minimal weight reduction of about 10 kg.

Although difficult to account exactly, the costs of our clinical work have never exceeded $30,000 a year. We feel the savings of occupational disability costs alone have more than justified this expense.

Conclusion

In our Veterans Administration setting, a sleep disorders clinic produced an extremely high yield of diagnostic information and therapeutic benefit. The percentage of patients in whom sleep apnea and nocturnal myoclonus were identified was higher in our health maintenance organization clinic than the percentage reported from fee-for-service clinics[6]; however, impressive percentages

of contributory recordings have also been described by clinics using private referral networks.[9] Our experience convinces us that sleep disorders clinics can play a worthwhile role in contemporary clinical practice.

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Platelet Markers of Thromboembolic Disease

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Platelets may be useful as markers of thromboembolic disease. When labeled with indium 111 they allow external imaging of localized clots. Indium 111 is much superior to chromium 51 for this procedure. Detection of circulating platelet aggregates also appears to be a simple means of determining the presence of thromboembolic disorders. In response to injury or involvement in clotting, platelets release several unique proteins not normally found in the plasma. Therefore, elevated levels of these proteins suggest the presence of such damage. Platelet factor 4 and β-thromboglobulin are the most widely studied of these proteins, and both can be quantitated by radioimmunoassay. Such assays are now commercially available. Elevated levels have been demonstrated in such diverse disorders as deep venous thrombosis, atherosclerosis and diabetes. However, blood must be drawn with great care to avoid in vitro damage to platelets and false elevation of these markers. All of these procedures are promising at present, but their precise role and value await further study.

THE DIAGNOSIS, TREATMENT AND PREVENTION of deep venous thrombosis (DVT) and pulmonary embolism (PE) continue to be major clinical problems. Their magnitude is illustrated by recent statistics: PE acounts for 50,000 deaths in the United States each year, and there are in excess of a half a million instances of PE in the same period.[1,2] It is the third most frequent cause of death,[3] being half as common as myocardial infarction and three times as frequent as cerebrovascular accident. PE may be responsible for one of every seven patient deaths in hospitals.[4]

Underdiagnosis remains a serious problem, despite increasingly sophisticated diagnostic procedures. For example, in the case of DVT, where clinical errors in diagnosis are startlingly frequent,[5] diagnostic procedures may include impedance plethysmography, Doppler ultrasound testing, radionuclide and contrast venography, and measurement of radioactively labeled fibrinogen uptake. For PE, in addition to x-ray studies of the chest and arterial oxygen tension measurements, there are ventilation and perfusion scanning and selective pulmonary angiography. Not all of these procedures can be considered routine, and certainly not all are readily available in every hospital. Often, several of them are carried out in the same patient, making accurate diagnosis expensive, time-consuming, inconvenient and not without risk. Many recent reviews and monographs[6-9] attest to the intense attention being paid to the evaluation of the proper role and accuracy

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ABBREVIATIONS USED IN TEXT

DVT = deep venous thrombosis
EDTA = ethylenediaminetetraacetic acid
LA-PF4 = low-affinity platelet factor 4
PE = pulmonary embolism
PF4 = platelet factor 4
βTG = β-thromboglobulin

of these procedures in the diagnosis of DVT and PE. Very recently, increasing interest has been devoted to the role of blood platelets in thromboembolic disorders and the use of platelets and substances released by them during activation and clotting as markers of thromboembolism. It is the purpose of this review to describe and evaluate these new procedures.

Platelet Physiology

Platelets are active and vital participants in the earliest phases of the hemostatic process. Circulating as individual cells, they are unaffected by normal endothelium. Once that endothelium is disrupted or altered, however, platelets stick to the exposed subendothelial fibrils of collagen and other materials (adhesion). The activated platelets also stick to each other, forming masses (cohesion or aggregation), which coalesce to form a platelet plug. As part of this process, platelets also make available certain materials which favor the initiation of blood clotting. The materials released from platelets during this process are numerous, and for our purposes can be termed unique or nonunique. Those which are unique are not normally found in plasma, and their presence there in significant quantities implies that platelets have released them due to injury or involvement in clotting. Therefore, such substances may serve as *markers* of the platelet release reaction. Indeed, platelets themselves may serve as such markers, by virtue of their property of adhering to each other, forming circulating aggregates or of adhering to newly formed clots in vessels. In the last instance, labeling platelets may allow detection of such new clots. In the following sections, each of these potential applications of platelets to the detection of in vivo clotting will be explored.

Platelets Labeled With Radioactive Materials

Platelets can be labeled with a variety of radioactive materials, including serotonin C 14, diisopropyl fluorophosphate P 32, methionine S 35, sodium sulfate S 35 and sodium chromate Cr 51. Only the last has been widely used for in vivo studies, which have included measurements of life span and turnover of platelets. Such measurements have shown that platelets are indeed damaged and contribute to reduced survival in patients with prosthetic heart valves, as shown by Harker and colleagues.[10,11] The same authors demonstrated that shortened survival could be improved by administration of dipyridamole, but not by aspirin. Unfortunately, the technique of measuring platelet survival and turnover by labeling platelets with ^{51}Cr is cumbersome. The number of platelets required is large—those derived from one unit of the patient's blood are generally needed, and the labeling efficiency is low. In addition, ^{51}Cr has a relatively long half-life of 27 days and, because of its low gamma photon emission at energies suitable for imaging, external detection of labeled platelets incorporated into in vivo clots is unsatisfactory.

Recently, a new label has been described, which has properties rendering it potentially far more useful for platelet labeling than ^{51}Cr. This isotope is indium 111, used as a chelate with 8-hydroxyquinoline (oxine). Introduced by Thakur and colleagues,[12] its properties are superior to ^{51}Cr. Its half-life is only 2.8 days, a tenth that of the chromium isotope. In addition, labeling efficiency is high, often better than 95 percent, so that fewer platelets are required. Its photon emission is such that it is ideal for gamma camera imaging. Results of studies in animals[13] and in humans[14] demonstrate that platelets labeled with this isotope accumulate rapidly in fresh emboli, allowing accurate mapping of their location. The same isotope has also been shown to provide information about platelet life span similar to that of ^{51}Cr.

Recent studies suggest that labeling platelets with ^{111}In is superior to the use of fibrinogen labeled with ^{125}I for the detection of early deep venous thrombosis.[15] However, the use of platelets labeled in this manner continues to be an experimental procedure. Its clinical value remains to be determined, particularly as its sensitivity, resolution and efficacy remain to be delineated in large scale studies in humans.

Platelet Aggregates

Wu and Hoak[16] introduced a relatively simple method for the detection and quantitation of platelet aggregates presumably formed and circulating in vivo. Venous blood is drawn into two separate tubes. One contains only ethylenedia-

minetetraacetic acid (EDTA) while the other contains EDTA plus formalin. In EDTA, no aggregates are found, as they are presumably broken up by this chelating agent. In the presence of formalin, the aggregates are rapidly fixed and cannot deaggregate despite the presence of EDTA. Platelet counts are done on each sample, and ratio of counts in the EDTA/formalin tube to that in the EDTA tube is calculated. In the absence of aggregates, the ratio is approximately one to one; that is, there is the same platelet count in each tube. In the presence of aggregates the platelet count in the EDTA/formalin tube is lower, and the ratio falls below one. The lower the ratio, the greater the number of aggregates. Technical considerations are important and may account for discrepancies.[17] The formalin must be freshly prepared and the counts carefully done. They can be done in whole blood using phase microscopy.

The presence of aggregates has been reported in patients with a variety of disorders, including thromboembolic disorders, transient ischemic attacks, myocardial infarction and migraine. Recently, Kumpuris and associates[18] described finding aggregates in patients with coronary artery disease during exercise. Ingestion of aspirin appeared to inhibit the development of these aggregates. The fact that platelet aggregates disappeared spontaneously within 30 minutes after exercise suggests that they were indeed induced by such exercise, although the mechanism is obscure. Even at rest, many of the patients studied had abnormal ratios. These findings are of particular interest in view of the finding by Green and coworkers[19] that platelets are activated during exercise-induced myocardial ischemia, a finding that will be reviewed in greater detail below. As with any new procedure, only extensive evaluation in a large number of subjects by a variety of investigators in various institutions will provide the data required for assessment of its clinical use.

Released Platelet Proteins

As noted above, the activation of platelets, either mechanically or by virtue of their involvement in coagulation, causes release of a variety of substances. A partial list is found in Figure 1, which differentiates those that are found in a variety of cells or fluids (nonunique) from those that are found only in platelets and are thus unique to that cell. Of particular interest are platelet factor 4 (PF4) and β-thromboglobulin (βTG), because these are the best characterized of the released factors and assays for each have been described. Indeed, sensitive radioimmunoassays for each of these proteins are available in commercial kits (PF4 from Abbott Laboratories, North Chicago, Illinois and βTG from Amersham Corp., Arlington Heights, Illinois). So-called low-affinity PF4 is also of interest, as it appears to be the precursor of βTG,[20] and cross-reacts immunologically with it. Some properties of each of these proteins are described in Table 1.

To use these proteins as markers of platelet release, their level must be measured in *plasma,* as opposed to serum. The latter represents the fluid remaining after blood clots; hence, the platelets have released a substantial proportion of their content of these proteins during the in vitro clotting process. Thus, the serum level is useless as a guide to the level of these proteins present in the plasma in vivo. Indeed, great pains must be taken to ensure that the blood specimen is collected under ideal conditions: a clean venipuncture, collection into an anticoagulant agent that contains EDTA (which inhibits release) and rapid chilling of the collection tube. The quality of the blood specimen is probably the single most im-

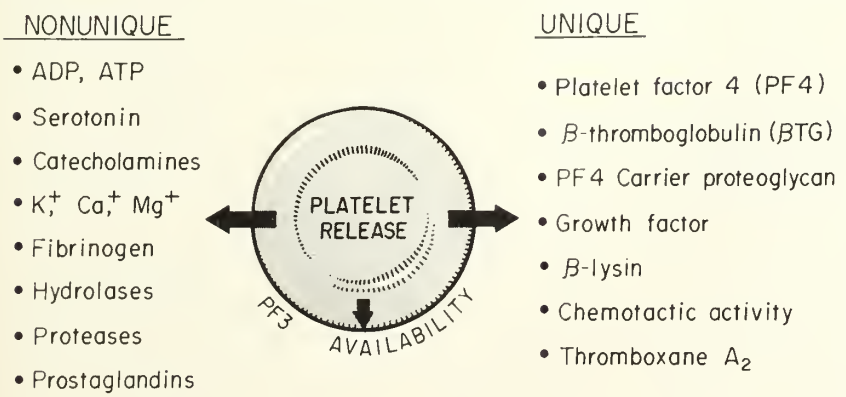

Figure 1.—Some materials released from platelets during coagulation. (ADP = adenosine dipthosphate; ATP = adenosine triphosphate; PF3 = platelet factor 3; PF4 = platelet factor 4; βTG = β-thromboglobulin.)

portant consideration in determining the clinical usefulness of these measurements. Some workers insist on using a two-syringe technique for collection of blood specimens, discarding the first few milliliters. Special anticoagulant agents are available, which may further inhibit in vitro release of these platelet proteins. Others feel that careful venipuncture and rapid chilling are the most important factors, and even the use of evacuated tubes for blood collection may be satisfactory under these conditions. It is clear that ideal blood collection is vital, but the precise conditions which allow one to determine that such ideal collection has been achieved are not yet in hand.

Platelet Factor 4

The existence of a substance in platelets capable of neutralizing heparin was suggested in 1948 by Conley and colleagues,[21] who noted a correlation of platelet count with the amount of heparin required by different patients. It was termed platelet factor 4 by van Creveld[22] and isolated by several workers using standard chemical procedures.[23,24] Recent isolation of PF4 by affinity chromatography on immobilized heparin allowed sufficient material to be isolated to permit detailed biochemical characterization, including amino acid sequencing.[25] It is a cationic protein, rich in lysine, which binds firmly to and instantaneously neutralizes, heparin. It is probably responsible for most of the ability of plasma, and certainly serum, to neutralize heparin. However, its level in plasma does not correlate well with the ability of a given plasma to affect a heparin-prolonged clotting time. The latter forms the basis of a clinical test introduced by O'Brien and colleagues.[26] Recent work indicates that PF4 may also exist on the endothelial surface, as large doses of heparin in humans cause prompt rise in plasma PF4, without evidence of platelet release.[27] As there is very little heparin present in plasma, the physiological role of this protein is uncertain, as is the role of other recently described biological activities of PF4, such as elastase enhancement and collagenase inhibition.[28,29]

β-thromboglobulin and Low Affinity PF4

Although the existence of a platelet-specific β-globulin had been reported previously, it was the work of Moore, Pepper and Cash[30] that resulted in the isolation and characterization of the protein they termed β-thromboglobulin. Recent study results suggest that it may actually be formed from low affinity PF4 (LA-PF4) outside the platelet after release, by enzymatic cleavage of the latter protein.[20] LA-PF4 is stored in the α-granule, as is PF4, and is released with it. The enzymatic action removes a few amino acids from one end of the molecule, thereby producing βTG. βTG and LA-PF4 are completely cross-reactive in immunoassays; hence, measurement by radioimmunoassay does not distinguish between them. No biological activity for either protein has been definitively described, and interest in them centers on their utility as markers for platelet release.

Clinical Studies

Elevated levels of βTG were first described in patients with deep venous thrombosis in 1975,[31] and it was suggested that such measurements may be of value in the diagnosis of that disorder. Since then, elevations in the plasma level of βTG, or PF4, or both have been described in a wide variety of clinical settings: myocardial infarc-

TABLE 1.—*Properties of Released Platelet Proteins*

	PF4	*Low-Affinity PF4*	*βTG*
Molecular weight	7,800	9,100	8,800
Storage site in platelet	α-granule	α-granule	α-granule
Biological activity	neutralizes heparin (enhances elastase, inhibits collagenase)	precursor of βTG	unknown
Half-time in plasma	short (5-10 minutes)	....	100 minutes
Assay	radioimmunoassay*; heparin-neutralizing ability	radioimmunoassay	radioimmunoassay*
Binding to heparin	strong	weak	weak
Normal level in plasma	10 ng/ml	....†	30 ng/ml
Normal level in serum	10,000 ng/ml	....†	30,000 ng/ml
Content in platelets	12 μg/10^9 platelets	20-25 μg/10^9 platelets	....†

PF4 = platelet factor 4; βTG = β-thromboglobulin

*Commercial radioimmunoassay kits available.
†Low-affinity PF4 and βTG cross-react in radioimmunoassy.

tion,[32] peripheral vascular disease,[33] diabetes mellitus,[34,35] myeloproliferative syndrome,[36] and transplant rejection.[37] More recently, Green and co-workers[19] demonstrated a transient rise in plasma levels of PF4 in patients with coronary artery disease during exercise testing. These studies indicate that damage to platelets may occur during exercise in some of these patients. However, we have been unable to confirm the results of Green and co-workers[41] in our own laboratory. It has been suggested that βTG levels may reflect only intravascular damage to platelets, as βTG levels are within normal range in patients with immune thrombocytopenia, but increased in disseminated intravascular coagulation and thrombotic thrombocytopenic purpura.[38]

Although it may be reasonable to accept elevated levels of these markers as evidence of platelet damage in disorders where such damage is expected, the finding of elevated levels in disorders such as multiple myeloma is disconcerting.[39]

Should these assays for platelet markers now be adopted for widespread clinical use? Is there a choice to be made between PF4 and βTG—that is, are they of equal use now that commercial kits are available for each? These are only a few of many questions difficult to answer. It is this writer's belief that further testing and development of these assays are necessary before their role can be determined. Technical problems in collection of blood have been mentioned above and continue to be a bar to a clear understanding of the significance of elevated levels. For those who wish to use these determinations, it should be emphasized that low levels are probably of greater significance than elevated ones, and may help to rule out the presence of relevant pathological conditions. Elevated levels must be confirmed by repeat determinations on additional blood specimens before being accepted at face value. Initial trials should be devoted to normal subjects to ensure adequate blood drawing procedure, which will be reflected in consistently low levels. As half-times of circulating PF4 are much shorter than those of βTG, it has been suggested that in vitro liberation of these markers may be reflected in proportional elevation of both PF4 and βTG. If release takes place in vivo, the βTG will remain relatively high while the PF4 will be lower. These considerations remain interesting but still theoretical. Whether either of these markers is preferable to others of nonplatelet origin, such as fragment E (derived from fibrinogen degradation),[40] remains to be seen. Until further clinical testing is carried out, caution should be the watchword.

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Epidemiology as a Guide to Clinical Decisions—II. Diet and Coronary Heart Disease

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Should clinicians prescribe fat-controlled diets to prevent coronary heart disease (CHD), and, if so, which patients should be given this advice? In this report, we use a three-step model to explain the hypothesis that dietary fats are a cause of CHD: dietary saturated fat and cholesterol raise serum cholesterol levels (step 1), which are a cause of subclinical coronary atherosclerosis (step 2), and, in turn, clinically manifest CHD (step 3). An evaluation of the scientific evidence for each step leads us to conclude that dietary fats definitely influence the level of serum cholesterol, and that serum cholesterol is probably a cause of atherosclerosis and CHD.

To determine the clinical implications, we examined the potential of various foods to keep cholesterol levels lower, as well as the projected magnitude of reduction in CHD risk. The likelihood of benefit varies among patients, ranging from uncertain or trivial (for those with lower serum cholesterol levels, those who are free of other risk factors and the elderly) to substantial (for patients with higher serum cholesterol levels, those who have other risk factors and those who are young). This analysis supports an individualized approach to clinical management; each decision to prescribe a fat-controlled diet should be a judgment that depends on art—the therapeutic philosophy of each clinician and the particular needs of each patient—as well as on science.

The implication for public health policies is that they should promote rather than a uniform eating pattern for all Americans, a uniform environment that enhances individual choices. This should include efforts to educate the medical profession and the public, and more comprehensive and informative food-labeling practices.

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ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein

THE SELECT COMMITTEE on Nutrition and Human Needs of the US Senate issued a report in 1977 specifying quantitative dietary goals for all Americans.[1] One of the report's most important recommendations was that Americans reduce their consumption of saturated fatty acids and cholesterol. The historic action of this congressional committee (no federal agency had previously endorsed the view that malnutrition might include *overconsumption* of food) was followed by similar statements from the Surgeon General[2] and from the Departments of Health, Education, and Welfare, and of Agriculture.[3] Together, these reports seemed to establish a public health policy on the role of fats in preventing coronary heart disease (CHD), one whose wisdom was confirmed by the conclusions of many recent reviews,[4-9] and by the recommendations of authorities[10] and professional groups[11] throughout the world.

The policy, however, has not met with uniform acceptance. While some of the opposing viewpoints[12] have been criticized for failing to meet rigorous scientific criteria,[6,13] others are more substantial.[14-18] The most notorious of these, the report of the National Academy of Sciences,[18] is representative; it opposes the universal promotion of fat-controlled diets on the grounds that the evidence for cause and effect is not yet conclusive. This point of view is difficult to dismiss because the evidence linking dietary fats to CHD is largely circumstantial. However, the evidence is also very extensive, and there is reason to believe that more convincing findings are not likely to be forthcoming. It is time to settle the matter.

In this report, we address the controversy as it bears on the practice of individual clinicians who must decide whether dietary prescriptions are likely to help their patients avoid heart disease. We present an evaluation of the scientific evidence for a cause-and-effect relationship between dietary fat and heart disease. We then discuss how clinicians might combine conclusions based on this evidence with their own individual treatment philosophies and the special needs of each patient in order to decide whether—and for whom—dietary intervention is desirable. We close with a note on the implications of this individualized approach for national health policy.

The Diet-Heart Hypothesis

The idea that dietary fat may be one of the causes of heart disease is referred to here as the diet-heart hypothesis. To examine the evidence with precision, we propose a three-step model (Figure 1): that saturated fats and cholesterol in the diet increase the level of serum cholesterol (step 1), and that higher serum cholesterol levels are a cause of coronary atherosclerosis (step 2) and coronary heart disease (step 3).* The model distinguishes between antecedent subclinical arteriosclerosis and clinically manifest CHD such as myocardial infarction.

Evaluating the Evidence

Judgments on the validity of each step of the diet-heart hypothesis are based on the three categories of evidence summarized in Table 1 and discussed below. Our focus is on the epidemiologic findings, and on the most informative citations selected from a larger body of published evidence.[7]

Nonepidemiologic studies. The general evidence bearing on the diet-heart hypothesis includes pathophysiological, clinical and animal studies.[5,7,19] Within the first set, the demonstration that atheromas contain cholesterol supports the validity of step 2, and the autopsy evidence for coronary arteriosclerosis as a general precursor of CHD supports step 3. Clinical studies of premature CHD in persons with rare lipid disorders such as familial hypercholesterolemia support steps 2 and 3. Ex-

*A more comprehensive formulation of the diet-heart hypothesis, with total cholesterol segregated into its lipoprotein fractions and roles proposed for salt and calories, is provided as an appendix. Because these additional factors do not substantially affect our conclusions, we will use Figure 1 (with total cholesterol as a proxy for low-density lipoprotein) to illustrate our reasoning.

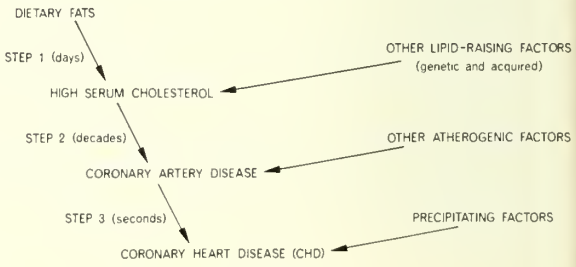

Figure 1.—Schematic diagram of the diet-lipid heart hypothesis. The arrows represent the proposed causal links between dietary fats, serum cholesterol level, subclinical atherosclerosis, and clinically manifest coronary heart disease (CHD). Two features that make it difficult to validate the hypothesis are the long duration of step 2 and the multifactorial causes of each step.

periments in animals prove that altering the fat composition of the diet can produce hypercholesterolemia and certain forms of coronary artery disease (steps 1 and 2).

These diverse lines of evidence provide biologic plausibility for the hypothesis, but they do not prove it; there is always some uncertainty in extrapolating the findings of laboratory studies to the clinical arena, or those of rare diseases to the general population. For this reason, the valuation "moderate" in Table 1 is often the maximum that the strength of causal inference from studies of this type can achieve.

Observational epidemiology. The science of epidemiology does not lend itself easily to the task of linking eating habits to chronic diseases. It is difficult to demonstrate, from statistical associations, causes that are remote in time and that are neither necessary nor sufficient.[5,7,20,21] Then there are special problems: the food we eat is complex and variable, dietary patterns are often confounded by other aspects of life-style, and it is difficult to measure eating habits accurately. Despite these barriers to drawing conclusions, population-based data are an indispensable component of preventive medicine decisions, and a reasonably convincing picture has now emerged from the many studies on the relationships between diet, lipids and heart disease. Table 1 summarizes this evidence according to the epidemiologic categories of place, time and person.

International studies[22-24] have shown that people living in countries where saturated fats and cholesterol are major components of the diet have relatively high average levels of serum cholesterol (step 1) and rates of CHD (steps 2 and 3 combined). Trends in the United States over the last several decades[25] have pointed to a weak association between national patterns of fat consumption and the average serum cholesterol level of population samples (step 1). Similarly, the average serum cholesterol level appears to have decreased in parallel with the current decline in the CHD rates of the nation (steps 2 and 3).

The well-known relationship between serum cholesterol level and subsequent incidence of CHD in cohort studies of individual persons is shown in Figure 2. The strength of this association, its dose-response characteristics and its consistency among studies[21,26,27] all support a causal basis for steps 2 and 3 combined. Evidence for step 2 alone is also found in autopsy[28] and angiographic[29] studies of coronary artery disease. Evidence to support step 1 has been elusive, and some studies have found no association between dietary fats and serum cholesterol level.[30] Although this finding has been cited as evidence against the diet-heart hypothesis,[12] it is more likely a false-negative (type 2 error) caused by the low precision and accuracy of techniques for assessing the dietary habits of populations.[31] Moreover, recent reports have offered positive evidence for step 1[32,33] and for the three steps combined.[33]

The chief barrier to confirming a causal relationship in these epidemiologic studies is the possibility that diet and CHD are both consequences

TABLE 1.—*Quality of Evidence Supporting the Validity of the Diet-Heart Hypothesis in the General Population*

	*Support for Causal Inference in Humans**		
Kind of Evidence	*Step 1: Diet Fats ↓ Serum Cholesterol*	*Step 2: Serum Cholesterol ↓ Coronary Arteriosclerosis*	*Step 3: Coronary Arteriosclerosis ↓ CHD*
Nonepidemiologic Evidence			
Pathophysiology studies	....	moderate	strong
Clinical studies of rare lipid disorders	....	moderate	moderate
Animal studies	moderate	moderate	....
Observational Epidemiology			
Place: International comparisons	moderate	moderate	
Time: Secular trends	mild	mild	
Person: Studies of individuals	mild	moderate	
Experimental Epidemiology			
Metabolic ward studies	strong	....	
Clinical trials of CHD prevention	strong	inconclusive	

CHD = coronary heart disease.

*The valuations are the judgments of the authors regarding, for each step, the strength of the evidence that a cause-and-effect relationship exists in general human populations.

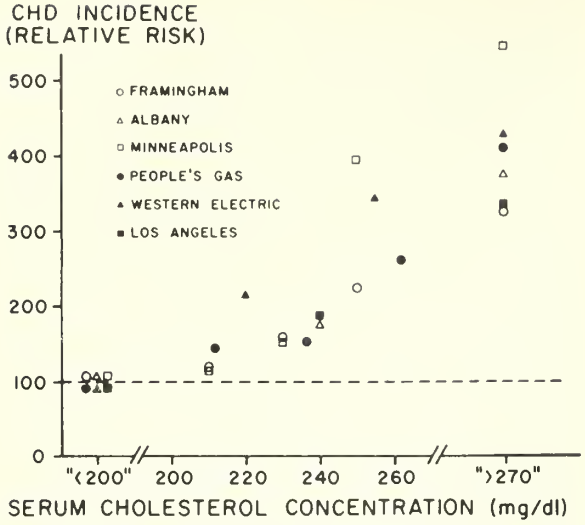

Figure 2.—Risk of developing coronary heart disease (CHD) in relation to preexisting serum cholesterol levels in six prospective epidemiologic studies. (Drawn from tabular data from Dayton et al.[26])

of some third (confounding) factor. However, this possibility has been made less likely in many of the studies cited above by showing that the observed associations are independent—that is, that they persist after adjusting statistically for other risk factors. But this calculation cannot indicate the possible influence of factors that were not measured. Observational epidemiology provides evidence that is circumstantial. For this reason, we have chosen the valuation "moderate" as the maximum in Table 1 that studies of this type can achieve.

Experimental epidemiology. How can we reduce this uncertainty? The classic resort is controlled clinical trials, a strategy capable of providing direct, rather than circumstantial, evidence. Such research, therefore, can provide a qualitatively different strength of causal inference.

Direct experimentation has been highly successful in resolving the uncertainty of step 1. Metabolic ward studies[34-36] and clinical trials of outpatients[37-39] have demonstrated conclusively that dietary composition governs serum cholesterol level. While other factors (notably heredity) influence this level as well, it is clear that dietary intake of cholesterol and saturated fats raises serum cholesterol levels, and that dietary intake of polyunsaturated fats decreases them.

Unfortunately, however, it has been more difficult to validate steps 2 and 3. Because of difficulties in measuring the extent of coronary artery disease under the circumstances of a clinical trial, we are forced to rely on the rate of CHD as the index of benefit. To be able to observe a change in this index, there must be a reasonable frequency of its occurrence; this means that the populations studied must be made up of persons who already have coronary artery disease. Even studies of this kind, which focus on a late stage of the disease and are, therefore, invariably a secondary form of prevention insofar as coronary arteriosclerosis is concerned, require that enormous numbers of participants be studied for a long time.

It should come as no surprise, then, that no definitive randomized trial of preventing CHD by dietary change has yet been carried out.[7,15,40,41] Of the studies that have been conducted, some have shown no benefit at all,[42,43] while others[39,44,45] have provided at best suggestive evidence for the efficacy of a fat-controlled diet. Some investigators have used cholesterol-lowering drugs as surrogates for dietary manipulation; such studies can take advantage of a double-blind design to guard against various biases. The major drug trials have not settled the issue, however. They have shown either no substantial benefit[46,47] or a reduction in CHD rates that was unexpectedly accompanied by an increase in overall mortality.[48]

In short, while we can conclude that reducing saturated fats and cholesterol in the diet does lower serum cholesterol levels, we have not yet established beyond doubt, probably because of technical barriers to conducting definitive research on the issue, that such diets will prevent heart disease.

Making a Judgment on Causality

Is this body of knowledge sufficient to establish policy on whether fat-controlled diets should be recommended to the American public? In our judgment, it is. The existing evidence, while circumstantial, is extensive and coherent in its support for the hypothesis. Furthermore, the prospects for stronger evidence emerging in the future are limited.

This is not to say that there will be no new information. Promising clinical trials in progress include a study of cholestyramine for preventing coronary arteriosclerosis[41] (which uses angiography to isolate step 2 data), and trials of cholestyramine[49] and intestinal bypass[50] for preventing CHD (steps 2 and 3 combined). These studies, however, are all surrogate tests in which a drug or an operation serves as a proxy for dietary change, and all involve a special group of par-

ticipants selected for their high levels of serum cholesterol. The only current tests of diet change per se address several risk factors simultaneously,[51,52] and these will only test the efficacy of the multifactor program as a whole. It is unlikely that a trial of diet alone will ever be undertaken, given barriers such as the estimated sample size (50,000) of such a study, unless novel approaches to design are developed.[53]

If new evidence in the foreseeable future is not likely to settle the matter conclusively, where does that leave us? Some experts propose that the residual uncertainty means that an intervention policy is not warranted. In our judgment, however, and in that of many others,[1-11,13] the evidence supporting the diet-heart hypothesis is sufficiently persuasive to justify active nutritional intervention now.

Developing a Nutritional Policy

Having reached the judgment that dietary fats are at least one of the causes of heart disease, we now turn to the practical aspects of developing and implementing a nutritional policy: What foods should be recommended to which patients?

The Projected Impact of Specified Foods on CHD

The general approach to dietary management of serum cholesterol levels is well known: Replace animal fats with vegetable products and, for those who are overweight, lower the intake of calories.[54] To decide which particular foods are most effective in lowering serum cholesterol levels, it is helpful to take a more quantitative approach.[55,56] By how much is serum cholesterol lowered (or raised) by various actual foods (step 1), and by how much is the risk of CHD lowered when serum cholesterol is reduced by a given amount (steps 2 and 3)?

Effects of foods on serum cholesterol level. The chief dietary precepts of a fat-controlled diet are illustrated in Table 2, where we provide examples of commonly eaten high-fat foods and low-fat alternatives. To estimate the relative importance of eating a low- rather than a high-fat food, we have calculated (based on metabolic ward data) the theoretical contribution to the serum cholesterol level if each food were eaten daily. The foods that raise serum cholesterol levels the most are those that have the highest amounts of saturated fat and cholesterol: meats and animal fat, organ meats, butter and egg yolks.

Effects of lowering serum cholesterol levels on

TABLE 2.—*General Precepts of a Fat-Controlled Diet, With Examples to Indicate the Relative Impact Each Food Change Might Have on Serum Cholesterol Levels*

General Precepts	*Example of a High-Fat Food**	*Approximate Contribution to Serum Cholesterol if Eaten Daily† (mg/dl)*	*Example of a Fat-Controlled Food*	*Approximate Contribution to Serum Cholesterol if Eaten Daily† (mg/dl)*	*Approximate Change in Serum Cholesterol Level (mg/dl)*
1. Trim all visible fat	6 oz untrimmed choice porterhouse steak	38	6 oz trimmed choice porterhouse steak	16	−22
2. Substitute fish or chicken for beef, pork & lamb	4 oz lamb chop	20	4 oz skinned chicken	7	−13
3. Eliminate organ meats (liver, kidney, heart, brain, and sweetbreads)	3 oz liver	28	3 oz tuna	5	−23
4. Substitute polyunsaturated oils for solid cooking fats and monounsaturated oils	1 oz bacon fat or lard	9	1 oz safflower oil	−9	−18
5. Substitute polyunsaturated margarine for butter	1 oz butter	15	1 oz polyunsaturated margarine	−2	−17
6. Substitute egg whites for whole eggs	1 whole egg	19	1 egg white	0	−19
7. Substitute low-fat desserts for ice cream	4 oz ice cream	8	4 oz skim yogurt	0	−8
8. Choose lean meats	4 oz hamburger (35% fat)	25	4 oz hamburger (10% fat)	12	−13
9. Substitute low-fat cheese for regular cheese	2 oz cheddar cheese	12	2 oz low-fat cheese	2	−10
10. Substitute skim milk for regular milk	½ pint whole milk	5	½ pint skim milk	0	−5

*The foods listed here were selected because they are common parts of the American diet and because they have a relatively strong influence in raising cholesterol levels. We have not included processed combinations of food (such as hot dogs), whose effects will depend on their ingredients, nor foods that are rare or have little influence on serum cholesterol. These have been presented in detail elsewhere.[54,55] Grains, fruits and vegetables are omitted because they do not raise serum cholesterol levels unless eaten in quantities sufficient to induce obesity (exception: coconut).

†The average contribution of each food, if it were eaten daily, is calculated as $2.16S - 1.65P + 0.0677C - 0.5$, where S = % of calories from saturated fat, P = % of calories from polyunsaturated fat, and C = mg of dietary cholesterol per day. This simplified formula is based on metabolic ward studies of the effects of varying dietary composition while calories are kept constant,[34,35] and it projects averages that do not reflect the possibility of biologic variability among individual persons in their responses to a given food.

TABLE 3.—*Mean Levels of Plasma Cholesterol in United States Populations Reported by the Lipid Research Clinics,* by Age and Sex*

Age (Years)	Plasma Cholesterol Level (mg/dl) Women	Men
20-24	162	162
25-29	174	179
30-34	174	193
35-39	188	201
40-44	196	205
45-49	205	213
50-54	222	213
55-59	231	215

*From Heiss et al.[62]

CHD risk. The beneficial effect of avoiding foods that increase levels of cholesterol can be projected from the cohort studies shown in Figure 2. The amount by which a person's risk changes will vary with the individual factors described below. On the average, however, a person with a moderately high initial serum cholesterol level (such as 250 mg per dl) has about a 1 percent lower risk of CHD for each 1 mg per dl decrease in the lipid level. In other words, dietary intervention that achieves a reduction in serum cholesterol of 25 mg per dl, may prevent (or postpone) a quarter of the CHD deaths in such persons.

This projection, however, may exaggerate the effectiveness of an intervention begun in the middle years of life when coronary arteriosclerosis is already established. It is also a relatively modest benefit when measured against the gains of 50 percent and more that may result from eliminating other major risk factors such as hypertension and smoking.[57] Nevertheless, larger reductions in cholesterol level (and CHD risk) would be likely to result from changing to extremely low-fat diets such as those recommended by Pritikin and eaten in many parts of the world.[58] Clearly, even a small reduction in risk would be considered worthwhile by many persons and would have an important impact on the health of the population as a whole.

Tailoring Dietary Advice to Particular Patients

It seems likely that some patients will benefit more than others from a fat-controlled diet; the following considerations are relevant to deciding who should receive such dietary advice.

Serum cholesterol level. The most useful index for deciding how extensive a fat-controlled diet to recommend is the serum cholesterol level. (Low-density lipoprotein cholesterol might be a more precise criterion [see appendix], but its theoretical advantages have been difficult to demonstrate in practice, and total cholesterol remains the more available, economic and familiar laboratory test.) Middle-aged patients with serum total-cholesterol levels higher than 210 mg per dl are more likely to benefit from dietary advice than those with lower levels because the risk-benefit ratio is marginal or conceivably adverse below this point; through cause and effect seems unlikely, low levels of serum cholesterol have been associated with increased risk of cancer and stroke.[59,60] Patients with very high cholesterol levels have the potential for a greater reduction in risk per unit of serum cholesterol lowered than do those with moderate levels, because the relationship between serum cholesterol level and CHD incidence seems to fit an exponential-type curve.[61]

The choice of 210 mg per dl for the cutoff point is a somewhat arbitrary interpretation of the data in Figure 2. The value is close to the population mean for middle-aged men and women. Because younger people tend to have lower levels, it seems reasonable to recommend that the persons who are likely to benefit substantially from dietary advice are those with plasma cholesterol levels (confirmed by testing on several occasions) that are above the mean for their age and sex. Population-based data for such decisions are provided in Table 3.

Other risk factors. Hypertension, cigarette smoking, low levels of high-density lipoprotein, physical inactivity, and male sex are relevant because of the multiplicative interaction of risk factors. This means that the amount of risk associated with a given increment in serum cholesterol concentration is increased in the presence of other risk factors.[56,57,61]

Age and prior heart attack. Young people seem to be an attractive target for dietary intervention because primary prevention can be started before atherogenesis begins, and also because dietary habits learned in childhood may persist for a lifetime. On the other hand, there are psychological and pragmatic drawbacks to focusing the attention of selected children on adult diseases.

The elderly are at particularly high risk, but altering serum cholesterol levels may not be effective if advanced coronary arteriosclerosis has already developed. Those who have already had a heart attack have a relative risk of recurrence for a given increment of serum cholesterol that is much smaller than that for first infarction,[63] due perhaps to the presence of advanced coronary

arteriosclerosis. However, this observation is biased by special selection factors that operate in studies of men who have already had heart attacks,[64] and the high overall level of risk for such patients means that even a small proportionate reduction in mortality may save many lives.

Conclusions

Scientific and Public Health Considerations

Our discussion thus far has dealt with the *science* of the diet-heart issue. We have shown that excessive dietary fat, eaten over a long time, is very likely to be a cause of heart disease. Further, that certain persons—particularly those above the 50th percentile of the population distribution with regards to serum cholesterol concentration and those with other risk factors—will probably have meaningful reductions in risk if they reduce their habitual intake of animal fat. At the same time, we suggest that there are also groups of people for whom such dietary intervention will be only marginally—if at all—beneficial.

The implications of these scientific judgments for public policy follow from the idea that, to be effective, public health measures should be applied uniformly to the entire population. We support existing nutrition guidelines[1-3] designed to educate the general public and to create a climate that encourages those people who choose to modify their diets. We propose the enactment of more informative food-labeling regulations that include a wider selection of foods and their ingredients and that specify quantities of saturated fat and cholesterol as well as standard nutrients. To that end, we believe that all foods—including meat, butter, eggs and other products listed on Table 2—should be sold with labels that enable consumers to estimate the potential increase of cholesterol level after eating an average serving. These policies will create an environment that supports an informed choice in eating habits throughout the population.

The Art of Medicine

We now turn to the *art* of applying these scientific judgments to the actual practice of medicine. At least two persons are involved in any clinical decision—the clinician and the patient. The decision to prescribe a low-fat diet depends on the individual characteristics of each.

The therapeutic philosophy of each *clinician* is based on years of educating and advising patients, and of observing the behavioral outcome. This experience creates a value system that will determine both the vigor of an intervention stance and the choice and method of presenting health information.

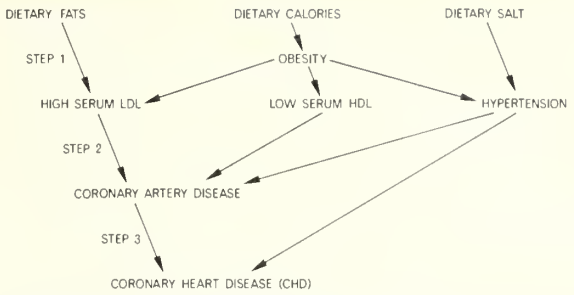

Figure 3.—Schematic representation of a more comprehensive diet-lipid-heart hypothesis, which presents lipoproteins in the place of total cholesterol and which includes proposed roles for dietary factors other than fats. (CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein)

The ultimate determinant of the clinical decision, however, is the individual preference of the *patient*. Many will welcome the opportunity to make dietary changes directed at their future health, even if the likelihood of benefit is small. Others may be unwilling or unable to alter their habits. The patient's family situation bears on the decision, for there are practical, cultural and, sometimes, medical advantages to a common eating pattern for an entire household. Virtually all patients like to think of food as a good and satisfying part of life, and dietary advice should be tempered to enhance this natural and rewarding goal.

We have attempted in this report to reduce the confusion created by conflicting dietary recommendations[1-18] by suggesting that dietary intervention is more appropriate in some circumstances than in others, and that clinicians should use their professional skills to tailor advice based on scientific considerations to the particular needs and beliefs of each patient.

Appendix

Additional Aspects of the Diet-Heart Hypothesis

A more comprehensive form of the diet-heart hypothesis is provided in Figure 3. Low-density lipoprotein (LDL), which carries most of the blood's cholesterol, occupies the same position as total cholesterol does in Figure 1; indeed, these two variables are usually comparable for clinical purposes.[65]

A growing body of evidence suggests that the

inverse relationship between high-density lipoprotein (HDL) levels and CHD incidence has a causal basis.[66] HDL does not bear on the discussion in this paper, however, because its relationship with CHD is independent of the LDL-CHD connection[65] and because those changes in dietary fat that lower the level of LDL- (or total-) cholesterol do not appear to influence HDL-cholesterol concentration.[67] The third major class of lipoproteins, those of very-low-density lipoprotein (VLDL), are not included in Figure 3 because the evidence that they are atherogenic is relatively weak.[21]

It appears that HDL and LDL are both determined in part by obesity.[54,67] However, the influence of calories on these two lipoproteins and on disease is beyond the scope of this paper, as is the concern with salt as a determinant of hypertension. Clinical decisions regarding calories and salt require the same combination of science and art noted in this report for advice on dietary fat. We refer readers to a recent review for the scientific facts necessary for this task.[7]

We should also note that dietary fats may have a role in the development of diseases other than CHD. The evidence for a causal connection between animal fats and cancer[68] is much less extensive than that discussed in this report, however, and we believe it is premature to use this rationale for recommending dietary changes.

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Refer to: Roberts JM: Preeclampsia and eclampsia—Medical Staff Conference, University of California, San Francisco. West J Med 135:34-43, Jul 1981

Preeclampsia and Eclampsia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *The topic of this Medical Grand Rounds is preeclampsia and eclampsia. Dr. Rhyner will begin the discussion by presenting a case.*

DR. RHYNER:† The patient is a 23-year-old woman (gravida 2, para 0, abortus 1) who at 36 weeks of pregnancy went to her physician because of increasingly severe headaches and visual blurring for two or three days. Her pregnancy had been uncomplicated, and she had no history of hypertension. During the examination she had a grand mal seizure. Findings of an initial evaluation included a blood pressure of 120/90 mm of mercury and proteinuria (3+). Treatment with magnesium sulfate was begun and she was transferred to this hospital. On admittance to the Obstetrics Service, the patient was awake and alert. Her blood pressure was 140/90 mm of mercury, with a heart rate of 90 beats per minute. Her fundi were benign and there was no thyromegaly. Her lungs were clear and there were no cardiac gallops or murmurs. Neurological examination showed that her reflexes were 4+ with bilateral clonus.

Laboratory data on admission included 13 grams of hemoglobin per dl, a hematocrit of 38.1 percent and 194,000 platelets per cu mm. Prothrombin time was normal at 11.2 seconds; fibrinogen was 293 mg per dl and fibrin-split products were 100 mg per dl. SMA-6 showed sodium 138, potassium 3.6, chloride 102 and bicarbonate 22 mEq per liter. Blood urea nitrogen was 12 and creatinine 1.1 mg per dl.

During the hospital course the patient underwent oxytocin- (Pitocin-) induced labor and gave birth to a 2,300 gram girl, with Apgar scores of 8 and 9. Magnesium sulfate therapy was continued for 24 hours and phenobarbital was added. Her blood pressure remained 130/80 mm of mercury and her reflexes were normal. Forty-eight hours after delivery she was noted to have tachycardia with a rate of 130 per minute. At this time, her blood pressure was 170/100 mm of mercury, and she was afebrile. On examination of her chest, left lower lobe rales were noted; results of an x-ray study of the chest showed a left lower lobe infiltrate and a small effusion. Blood gases while breathing room air showed a pH of 7.49, oxygen pressure (Po_2) of 42 and carbon dioxide pressure (Pco_2) of 34 mm of mercury. Bilateral rales and a gallop rhythm rapidly developed and repeat x-ray films of the chest showed the development of large bilateral pleural effusions and pulmonary edema. Findings of a lung scan were negative. The pleural fluid was a transudate. Tests for anti-double-stranded DNA antibody, fibrin-split products and fibrinogen were negative. She was transferred to the coronary care unit where hemodynamic monitoring showed a right atrial pressure

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†Patricia Rhyner, MD, Medical Resident.

of 8, a pulmonary capillary wedge of 28 and pulmonary artery pressure of 35/20 mm of mercury; her cardiac output was 5.3 liters per minute. Cardiac function was within normal range, based on results of an echocardiogram. She was treated with supplemental oxygen, nitroprusside, furosemide (Lasix) and propranolol. At discharge, her blood pressure was 120/70 mm of mercury, her gallop rhythm had resolved and blood gases while breathing room air showed a pH of 7.39, P_{O_2} of 81 and a P_{CO_2} of 43 mm of mercury.

DR. NAUGHTON: *Next, Dr. James Roberts of the Department of Obstetrics and Gynecology will discuss preeclampsia-eclampsia from a perspective relevant to nonobstretricians.*

DR. ROBERTS:* The patient described above manifested a challenging and fascinating clinical problem, preeclampsia-eclampsia. The disease is challenging because it tests both the medical and obstetrical skills of the clinicians involved. Our medical skills are tested by the derangements of many physiological processes. For example, in our patient there was evidence of a central nervous system abnormality manifested by convulsions, and changes in renal function indicated by a serum creatinine concentration of 1.1 mg per dl (decidedly elevated for a woman in late pregnancy). In addition, there was evidence of disseminated intravenous coagulation with elevated fibrin-split products and decreased platelets and fibrinogen, compared with normal values during pregnancy. If liver function had been tested, I am sure that it would have been found to be abnormal as well. The most significant physiological derangement for this woman was pulmonary edema, a condition that is not seen frequently in women with preeclampsia-eclampsia. The incidence of pulmonary edema is probably less than 10 percent. This is fortunate because the mortality rate reported for eclampsia complicated by pulmonary edema is high.[1]

Hemodynamic changes in women with eclampsia and pulmonary edema have not been studied extensively. In the few women in whom such changes were documented, the changes were similar to those in our patient. In other patients relatively normal indexes were noted when Swan-Ganz catheters were inserted.[2] The cause of this condition has not been determined. One possible explanation is that normally there is a massive mobilization of interstitial fluid 24 to 48 hours postpartum in women with preeclampsia. This usually results in a dramatic diuresis; however, occasionally the increased intravascular volume is not tolerated and results in pulmonary edema. In some cases, the fluid mobilization is not tolerated because the patient has substantial oliguria due to renal effects of preeclampsia. In patients with pulmonary edema that I have seen previously, this has been the usual inciting factor. In our patient it is difficult to determine whether renal problems or an intrinsic cardiac defect accounted for inability to tolerate this fluid shift or whether the congestive heart failure was in some way related to the profound vasospasm present in eclampsia. However, it is obvious that the use of hemodynamic monitoring and an appropriate approach to management resulted in a benign course. I suspect that the reported high mortality of pulmonary edema related to eclampsia would be less if the above approaches were attempted.

Another interesting point in this case is the fact that the patient's blood pressure was not exceptionally elevated—the highest diastolic pressure recorded was 100 mm of mercury—in spite of the fact that she manifested many physiological derangements. This is an important feature of preeclampsia, which I will discuss in some detail.

Preeclampsia-eclampsia is challenging to obstetricians. Attempts to palliate the mother's medical condition with the baby *in utero* must be done with the knowledge that treatment may compromise the fetus, either directly or, more important, by effects on uterine blood flow. Once a woman is eclamptic, delivery is almost always an appropriate management. Another obstetrical challenge in the management of patients seeking medical attention at earlier stages of this disease is to determine whether the fetus, which is at increased risk, is safer remaining *in utero* or being delivered; certainly in this woman there was no question. Obstetricians are faced with a critical decision in determining whether to induce delivery of the fetus.

I mentioned above the fascinating nature of preeclampsia-eclampsia. At least part of this is because no clear-cut cause has been determined other than the fact that the women with the disorder are pregnant. It is also intriguing that the impressive derangements of physiological function that occur all return to normal with the termination of pregnancy.

Over the years varying forms of nomenclature

*James M. Roberts, MD, Associate Professor of Obstetrics and Gynecology.

TABLE 1.—*Hypertensive Disorders in Pregnancy*

Chronic hypertensive disease
Blood pressure >140/90 mm of mercury before 20 weeks of gestation
Preeclampsia-eclampsia
Blood pressure elevation >15 mm of mercury diastolic or 30 mm of mercury systolic
Proteinuria >0.3 gram/24 hours
Edema

have been used to differentiate women who are already hypertensive and then become pregnant from those who have preeclampsia-eclampsia (Table 1). It is assumed that if a woman has an elevated blood pressure of greater than 140/90 mm of mercury before 20 weeks gestation, she was hypertensive before pregnancy. This aspect of the diagnosis is becoming easier to confirm because today many women know their blood pressure before they become pregnant. Preeclampsia-eclampsia is characterized not by a fixed elevated blood pressure but by blood pressure increases, 15 mm of mercury diastolic or 30 mm of mercury systolic, over values recorded in early pregnancy.[3] It is likely that this occurred in our patient because most young women in early pregnancy will have blood pressures in the range of 110/60.

In addition to blood pressure elevation, patients with preeclampsia-eclampsia frequently have proteinuria, which is defined as the excretion of more than 0.3 gram of protein per 24 hours, and sodium retention that leads to edema. The disease primarily involves women in their first pregnancy —two thirds of all cases occur within this group. There is a wide range in the severity of the disease. Some cases just barely satisfy diagnostic criteria of blood pressure, proteinuria or edema (or a combination of two of these); others involve more substantial blood pressure elevation and proteinuria, and, finally, the most serious cases involve seizures as well.

The diagnosis of preeclampsia is based on the presence of at least two of the three criteria—elevated blood pressure, edema and proteinuria. Eclampsia is preeclampsia plus convulsions. It is important to realize that women do not become eclamptic de novo but rather progress from being mildly preeclamptic to more severely preeclamptic to eclamptic. Because the vast majority of patients with mild-to-moderate eclampsia are asymptomatic, attempts to recognize mild preeclampsia before it progresses to eclampsia necessitate frequent obstetrical visits in late pregnancy. This progression can occur slowly over time such that the mild preeclampsia develops and the woman's condition changes minimally over the remainder of her pregnancy. Or, it may progress quickly so that the woman is mildly preeclamptic at 34 weeks of gestation and severely preeclamptic at 38 weeks or, in the most frightening of cases, the spectrum can be traversed rapidly—in a matter of days. Obstetrical management in late pregnancy should be directed at trying to identify women who are preeclamptic in order to recognize any patient whose condition is rapidly worsening.

I will now discuss the pathological and pathophysiological changes that occur[3] and the philosophy of obstetric management, especially the question of the short-term and long-term prognoses of the mother and baby. I will also discuss the rationale for the pharmacological agents that are used in the management of severely preeclamptic women and the necessity of follow-up.

Preeclampsia is not just elevated blood pressure or an unmasking of essential hypertension. It is a disease with manifestations that are very different than those in women who are hypertensive before pregnancy. Most obstetricians who deal with preeclampsia feel that from a clinical point of view, blood pressure elevation alone is not the most important pathophysiological factor. Frequently, as in our patient's case, women with preeclampsia will have multisystem disease with blood pressure measurements that are not at a level usually associated with any symptoms. This impression from clinical observation is supported by pathological changes that occur in women who die of eclampsia.[3] The common denominator is that the changes seem not to involve blood vessel disruption but rather are changes associated with poor tissue perfusion, such as periportal hepatic necrosis and hemorrhage and necrosis in the heart and adrenal glands. Even though cerebral hemorrhage is common, massive cerebral hemorrhage occurs in only 10 percent to 15 percent of women dying of eclampsia. Most patients have intracranial petechial hemorrhages, which are usually associated with asphyxia or poor perfusion.

In preeclampsia-eclampsia there is decreased perfusion to a number of vital organs, including the liver, kidney, brain and, very importantly, the uterus and choriodecidual space (Table 2). The last change is of prime importance because fetal well-being may be substantially compromised. Evaluating other cardiovascular variables (Table

TABLE 2.—*Regional Blood Flow Changes in Normal Pregnancy and in Preeclampsia-Eclampsia*

	Normal Pregnancy vs. Nonpregnancy	*Preeclampsia-Eclampsia vs. Normal Pregnancy*
Liver	→	↓
Kidney	↑	↓
Cerebral	→	→
Extremity blood flow	→	→
Uterus	↑	↓
Choriodecidual space	..	↓

→ = no change; ↑ = increased; ↓ = decreased.

TABLE 3.—*Cardiovascular Changes in Preeclampsia-Eclampsia*

	Normal Pregnancy vs. Nonpregnancy	*Preeclampsia-Eclampsia vs. Normal Pregnancy*
Plasma volume	↑	↓
Red blood cell volume	↑	↓
Cardiac output	↑	→
Total peripheral resistance	↓	↑

↑ = increased; ↓ = decreased; → = no change.

3) indicates that cardiac output is unchanged. Therefore, the increased blood pressure is due to increased total peripheral resistance, suggesting that the poor perfusion may be the result of vasospasm. Changes of red blood cell mass and plasma volume are similar to those present in persons with end-stage shock and massive vasoconstriction. On the basis of these findings, it is evident that the blood pressure changes that occur in preeclampsia are secondary to a vasospastic process that has as its most important manifestation a decrease in perfusion of a number of vital organs. It does not seem that the elevation of blood pressure per se brings about the damage. There is also a dramatic decrease in the renal glomerular filtration rate in preeclamptic women compared with normal pregnant women. This is an almost universal finding. A large part of the decreased glomerular filtration rate is explained by changes in renal blood flow. The change is not entirely explained by this, however, since the filtration fraction is also decreased. Uric acid clearance is decreased and, thus, hyperuricemia becomes one of the most reliable laboratory tests to differentiate preeclampsia from essential hypertension. Renal tubular function remains relatively normal, but the decreased glomerular filtration rate results in decreased delivery of sodium to tubules that continue to reabsorb sodium at a normal rate. The imbalance between glomerular and tubular function results in sodium retention. This retention does not require the existence of excess of a known or unknown mineralocorticoid. Changes visualized in renal biopsy specimens of preeclamptic patients again emphasize that preeclampsia is not simply essential hypertension[4,5] (Figure 1). The capillary lumen of the glomeruli from kidneys of preeclamptic women is occluded by swollen endothelial cells. The basement membrane contains inclusions but is otherwise relatively normal. The epithelial foot

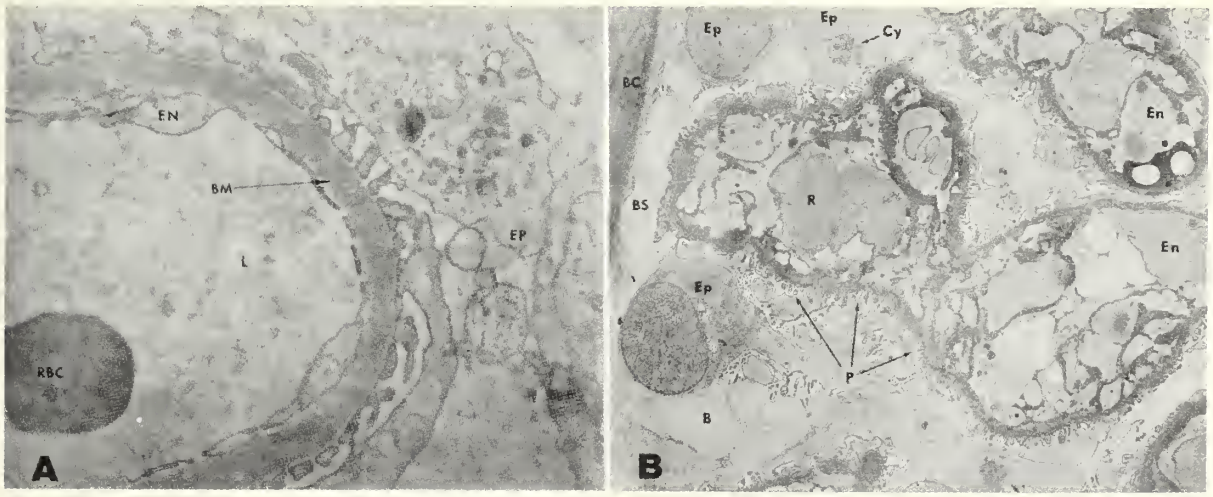

Figure 1.—Electron photomicrographs of renal biopsy specimens from normal **(A)** and preeclamptic **(B)** pregnant women: **A,** Glomerulus of normal pregnant woman. (RBC = red blood cell, EN = endothelial cell, L = capillary lumen, BM = glomerular capillary basement membrane, EP = renal epithelial cell.) (From McCartney.[4]) **B,** Glomerulus of preeclamptic woman. (R = red blood cell [in capillary lumen], En = endothelial cell, Ep = epithelial cells, P = epithelial cell podocytes, Cy = cytoplasmic inclusions.) Note that capillary lumen is virtually occluded by endothelial cells, which are swollen and contain inclusions, but that epithelial foot processes are normal. (From Faith and Trump.[5])

processes also appear to be normal. This finding is termed glomerular endotheliosis and can account for the decreased glomerular filtration that occurs beyond that caused by decreased renal blood flow. On the basis of the information presented, it appears that hypertension and sodium retention are secondary changes rather than primary pathogenic factors in the disease.

There is other recent information regarding the pathogenesis of preeclampsia that explains a number of clinical observations. Women in whom preeclampsia develops very quickly, over 24 to 48 hours, frequently give birth to babies that are severely growth retarded. Therefore, uterine perfusion was decreased long before the disease was clinically evident. Recent studies emphasize that the pathogenic changes antedate the clinical diagnosis of preeclampsia. It has been known for some time that women with preeclampsia are highly sensitive to any pressor agent.[6] They are more sensitive to norepinephrine or vasopressin, but the most impressive difference is seen in responsiveness to angiotensin. When one compares angiotensin responsiveness in normal pregnant women with that in women who are not pregnant, the normal pregnant women are actually less sensitive. Studies from Gant and co-workers[7] showed that the increased sensitivity to angiotensin precedes clinical preeclampsia (Figure 2). Increased sensitivity to angiotensin II is present as early as 14 weeks of gestation, while the clinical diagnosis of preeclampsia is not usually evident until 28 to 30 weeks of gestation. Other evidence for the existence of preeclampsia, before clinical diagnosis, can be obtained by carefully monitoring blood pressure throughout gestation (Figure 3). As early as 17 weeks gestation, the blood pressure measurements of most women who will become preeclamptic are already higher than those of women who will not.[8] Although the difference is statistically significant, the overlap, unfortunately, is too great to allow prediction in a given patient.

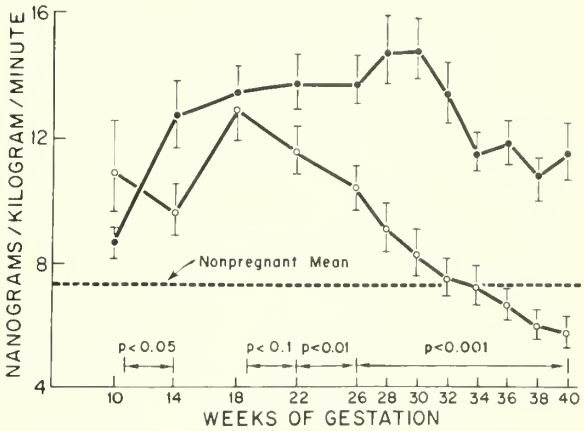

Figure 2.—Angiotensin sensitivity: Comparison of the angiotensin II dose (ng/kg/min) necessary to raise the diastolic pressure 20 mm of mercury in 120 women who remained normotensive (•) and 72 women in whom increased blood pressure developed in late gestation (o). (From Gant et al.[7])

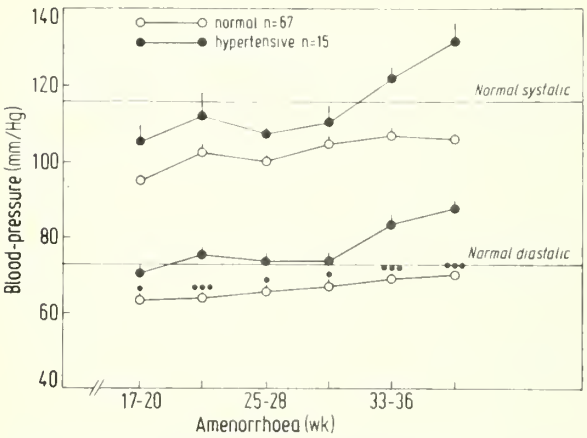

Figure 3.—Blood pressure at different gestational ages: Pregnant women had their blood pressure carefully measured through gestation. Average blood pressure of women in whom elevated blood pressure developed in late gestation (•) are compared with women who remained normotensive (o). Differences were statistically significant as early as 17 weeks gestation (•$P<0.05$; •••$P<0.001$). (From Gallery et al.[8])

We must consider the impact of the disease on mother and baby. Preeclampsia is very rarely associated with maternal mortality. However, if a woman becomes eclamptic, her risk of dying is about 3 percent to 5 percent.[3] Although this percentage does not represent a high mortality rate compared with certain other diseases that one deals with in medical practice, this figure is frightening when we consider that these are young healthy women with a completely reversible disease process. Moreover, the fetus is at increased risk even in a woman with preeclampsia. This infant has about five times the chance of dying as an infant of a mother who does not have this disease. That fivefold increase exists regardless of when in gestation the fetus is delivered.[9] If the woman becomes eclamptic, the perinatal mortality rate increases to approximately 20 percent. Thus, the disease presents a much greater risk of death to the fetus than to the mother.

In making management decisions, we must also consider the long-range outcome for the mother.

The relationship of preeclampsia to the development of hypertension in subsequent years is controversial. Virtually every study that has followed previously preeclamptic women for many years has concluded that the incidence of hypertension is increased in later life.[10,11] It is important to try to determine whether preeclampsia unmasks a hypertensive problem that was already present or whether preeclampsia occurs because the woman has an independent problem that increases the risk of developing both preeclampsia and hypertension in later years. Is it possible that preeclampsia damages kidneys or blood vessels and causes a woman, who would have been normotensive 20 years later, to become hypertensive?

The normal blood pressure changes of pregnancy lead to problems in the diagnosis of preeclampsia and in determining the long-range prognosis of preeclampsia[12] (Figure 4). In early pregnancy both diastolic and systolic blood pressures decrease by about 7 mm of mercury. This is the average; thus, in some women blood pressure will decrease to a greater extent. In our experience, it appears that in women who are hypertensive before pregnancy, blood pressure will decrease by more than 7 mm of mercury. For example, if a woman with undiagnosed hypertension did have a blood pressure decrease of 15 mm of mercury diastolic in early gestation, she would be considered normotensive at this time. When her blood pressure increased to its usual levels in late pregnancy, she would be diagnosed as preeclamptic. When she was seen post partum with her usual elevated blood pressure, it would be judged that her preeclampsia had resulted in persistent hypertension.

This difficulty in diagnosis can be illustrated by examining renal biopsy specimens of preeclamptic women (Table 4). Results of renal biopsies of women with preeclampsia during their first pregnancy indicate that about 70 percent will have glomerular endotheliosis, the lesion I discussed earlier. However, 25 percent of these women will also have evidence of underlying renal disease that was not suspected before the renal biopsy.[4] When renal biopsy specimens from women who have preeclampsia during later pregnancies are examined, very few of them demonstrate glomerular endotheliosis, but many have evidence for underlying renal disease or preexisting hypertension that was not previously recognized (Table 4). Thus, preeclampsia is a difficult disease to diagnose.

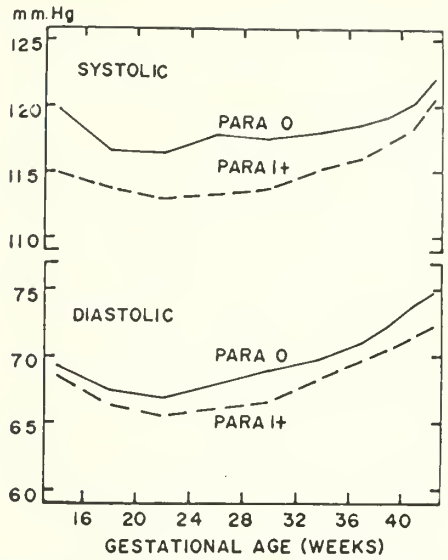

Figure 4.—Blood pressure during pregnancy: Mean blood pressure by gestational age of 6,662 white women who delivered single infants alive at term. (From Christianson.[12])

It is possible that the increased incidence of hypertension in later life in women who have had preeclampsia is due to inaccurate diagnosis. It is also possible, however, that a number of these women might not have become hypertensive had they not had preeclampsia. These possibilities have been successfully investigated in a study carried out by Leon Chesley.[13] This masterful study will probably never be repeated. He has followed a group of approximately 200 women who had eclampia in their first pregnancy. He chose eclamptic patients because he reasoned that if they were eclamptic and had seizures, they certainly had preeclampsia. They might have had other underlying diseases as well, but at least he

TABLE 4.—*Renal Biopsy Diagnoses of Patients With Clinical Diagnosis of Preeclampsia**

	Percent
Primigravida (62 patients)	
"Toxemic lesion"	70
Normal histology	5
Chronic renal disease (chronic GTN, chronic pyelonephritis)	25
Multigravida (152 patients)	
"Toxemic lesion" (with or without nephrosclerosis	14
Arteriolar nephrosclerosis	12
Normal histology	53
Chronic renal disease (chronic GTN, chronic pyelonephritis)	21

GTN = glomerulotubulonephritis

*Adapted from McCartney.[4]

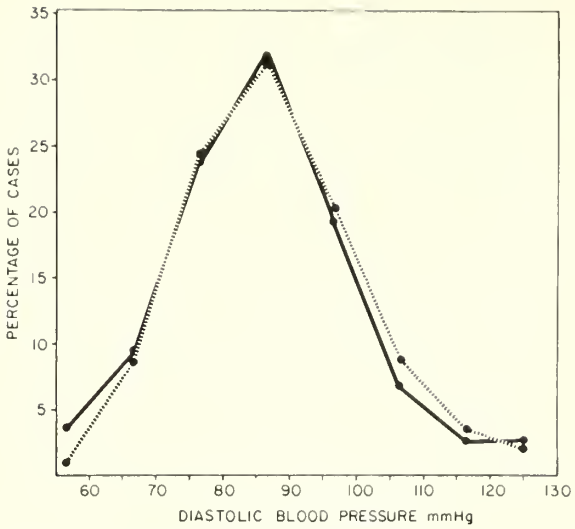

Figure 5.—Distribution of blood pressures in later life of primiparous women who had had eclampsia: Blood pressure distribution of 206 women who had had eclampsia in their first pregnancy (•—•), an average of 25 years after that pregnancy compared with 2,445 women matched for age and race from the Framingham study (•----•). (From Chesley et al.[13])

could be sure he was not dealing with women whose usually elevated blood pressure had become evident once again in late pregnancy. He followed these women for 42 years; two patients were lost to follow-up (Figure 5). I present the 25-year follow-up because at 25 years, women from the Framingham study could be an appropriate control group; however, beyond 25 years Chesley no longer had valid control groups for these elderly women. Comparing blood pressure distribution in the formerly eclamptic women with that of the controls shows that the distributions were identical. No matter how hypertension was defined, the incidence of hypertension was not increased in women who had been eclamptic during their first pregnancy, indicating that the eclampsia did not cause damage that led to hypertension in later life. Those women who became hypertensive were already destined to become so.

Let us use this information to attempt to formulate a philosophy of management. The most appropriate management would, of course, be to prevent the condition. This is not possible at present because we do not know what causes the disease. We do know the condition is more common among women of lower socioeconomic classes. Attempts have been made to link nutrition or vitamins to preeclampsia. Pregnant women have been starved, had their salt intake restricted or increased, fed high (or low) carbohydrate or high protein diets.[11] None of these treatments has been successful in preventing preeclampsia. We are able, however, to prevent preeclampsia from developing into eclampsia. Because the termination of the disease occurs with the termination of pregnancy, this preventive approach is possible.

Thus, we are forced to adopt a philosophy of management that uses the little information we do have to approach the condition rationally. It is important to remember that the signs and symptoms of the disease—blood pressure elevation and sodium retention—are not causal abnormalities. Also, because delivery will prevent a preeclamptic woman from becoming eclamptic and maternal deaths from the condition are limited to women with eclampsia, we would have a very efficient form of therapy if all we were considering was maternal well-being. However, for a woman with mild preeclampsia and a baby ten weeks before term, it is not always appropriate treatment for the fetus. I emphasize this because when considering advances in therapy, we must use as the indicator of successful therapy, not blood pressure changes or the effects on sodium retention, but the effect of the treatment on fetal well-being. If we use pharmacological agents or dietary manipulations to manage preeclampsia, the end point of successful therapy must be improved perinatal survival. Unfortunately, attempts to manage the disease pharmacologically—whether the pharmacological approach is something as irrational as diuresis in a woman whose plasma volume is already depleted, or whether it is lowering blood pressure because this is something we can measure, or even if it is therapy that seems rationally based on an attempt to increase blood flow to a number of important organs—have never improved fetal survival. I think the explanation is that the condition is present long before we make the clinical diagnosis and that there are probably already irreversible changes by this time. Thus, appropriate therapy might increase uterine blood flow, but there could already be vascular changes that prevent the increased uterine blood flow from being translated into increased placental perfusion.

The approach that obstetricians should take is to decide whether the fetus is at greater risk if left in utero or delivered. Fortunately, today there are tests that allow evaluation of the intrauterine fetus. These tests of biophysical functions, which evaluate fetal heart rate changes in response to fetal movement and uterine contraction, are fairly

reliable indicators of fetal well-being.[15] Analysis of amniotic fluid surfactant content also provides a reliable indicator of fetal lung maturation.[16] Because the major cause of death for premature infants is respiratory disease secondary to decreased surface-active material, this analysis permits determination of the risk of delivery to the infant. Using these tests, an obstetrician may rationally weigh the risk to the fetus in utero against the risk of prematurity. If delivery is elected, it is important to realize that it will terminate the disease but not abruptly. In the case presented here, congestive heart failure developed and the woman was still hypertensive 48 hours post partum. Delivery institutes the resolution of the disease but does not abruptly cure it. Also, the medical condition must be managed in a way that allows delivery without putting the woman at increased risk.

The two major objectives of therapy are prevention of convulsions and, in an occasional patient, the lowering of blood pressure. The prevention of convulsions requires the prophylactic use of an anticonvulsant agent for women who are severely preeclamptic or who have had seizures. It is also used for women with mild preeclampsia because the condition is more likely to accelerate during labor than at any other time. The anticonvulsant agent that is usually used is magnesium sulfate. This drug has not been chosen because it has dramatic effects on uterine blood flow, or has specific hypotensive effects in the doses used, or is the most effective anticonvulsant agent, or the most specific against eclamptic convulsions. Rather, it is used because when given in therapeutic doses, its impact on the fetus is less than that of the other agents that have been used in the past. This has been demonstrated by the work of Pritchard and Pritchard,[17] who treated eclampsia with magnesium sulfate in pregnancies involving 122 fetuses (Table 5). Among the fetuses that weighed more than 1,800 grams at the time eclampsia was diagnosed, there were no perinatal deaths. This is the standard against which all other approaches to anticonvulsant therapy during pregnancy must be judged.

When I first moved from internal medicine to obstetrics, I was appalled at using a drug—magnesium sulfate—that I had only known previously as a cathartic or an agent for animal euthanasia in the physiology laboratory. However, based on the considerations presented, it is a rational approach to therapy and safe when used appropriately. It is, however, a potentially lethal drug, the most serious problems being cardiac arrest and respiratory paralysis (Table 6).[18] These occur at serum concentrations above therapeutic levels. Empiric dosage schedules have been developed[3] that use either intramuscular or intravenous therapy or a combination of both. The initial dose recommended in these schedules is safe in all women regardless of renal function because the initially administered magnesium is diluted by distribution.[19] However, once the woman has received the initial dose of this drug, it is important to pay attention to urinary output because magnesium is excreted solely by the kidney. In women with adequate urinary output, the empiric approaches are safe and the levels of magnesium are judged grossly by following deep tendon reflexes. Deep tendon reflexes are lost at 10 mEq per liter, and the toxic effects occur above about 15 mEq per liter. A woman who has not lost deep tendon reflexes and has adequate urine output can safely continue to receive magnesium by the empiric dosage schedules. However, if urine output is less than 40 ml per hour or deep tendon reflexes are absent, therapy must be guided by measuring serum magnesium levels.

While anticonvulsant prophylaxis is used in all patients, only occasional patients will require antihypertensive therapy. Certainly, it would be diffi-

TABLE 5.—*Eclampsia: Fate of Fetuses Weighing 1,000 Grams or More at Parkland Memorial Hospital, 1955-1975**

	No. of Fetuses
Total in study	122
Dead when eclampsia diagnosed	7
Alive when eclampsia diagnosed	115
Intrapartum death	1†
Born alive	114
Neonatal deaths	4‡
Survived	110

*Adapted from Pritchard and Pritchard.[17]

†Fetus weighing 1,200 grams.

‡All weighed less than 1,800 grams; all 100 fetuses weighing 1,800 grams (4 pounds) or more and alive when eclampsia diagnosed survived.

TABLE 6.—*Effects of Magnesium Sulfate Given in Increasing Doses*

Effects	*Dose (mEq/liter)*
Therapeutic level	4-6
Electrocardiographic changes	5-10
Loss of deep tendon reflexes	10
Respiratory paralysis	15
General anesthesia	15
Cardiac arrest	>25

cult to argue that before our patient went into congestive failure, lowering her blood pressure was an important part of management. We use antihypertensive agents when blood pressure elevation is to a degree that increases the risk of intracranial bleeding. Antihypertensive therapy is used in women with diastolic pressures that are consistently greater than 110 mm of mercury. An agent must be chosen that will rapidly lower blood pressure, given the special considerations of safety of the fetus (Table 7). Trimethaphan is not used because it decreases cardiac output and uterine blood flow. Also, pregnant women are exquisitely sensitive to ganglionic blockers. Studies using animals indicate that sodium nitroprusside presents the same problem to the fetus as has been reported for adults receiving the drug; that is, with large doses given over a long time, serum thiocyanate concentrations increase. Diazoxide has been used extensively in pregnancy. However, we choose not to use it for the following reasons: (1) least important, it has effects on fetal carbohydrate metabolism; (2) if blood pressure of pregnant animals is lowered with diazoxide, uterine blood flow decreases and (3) most important, it works too well. If blood pressure is lowered too much with diazoxide, the drug is present for a number of hours; during that time uterine blood flow is decreased with no good way to increase uterine perfusion. The antihypertensive drug that we choose to use is hydralazine, administered intravenously. The choice of hydralazine is not based on the fact that it is very good for uterine blood flow of pregnant hypertensive sheep, but primarily because it is not nearly as potent an agent as diazoxide, and "overshoot" is very unlikely. The goal of antihypertensive therapy in these acute cases is not to lower the blood pressure to its usual levels but rather to a level that will reduce the likelihood of intracranial bleeding. For this goal hydralazine is very effective. Because the maximal effect of the drug is about 20 minutes after administration and the duration of action is three to eight hours, a continuous intravenous infusion does not seem reasonable. Therefore, we administer the drug intravenously as a 5-mg bolus and repeat this every 20 minutes as necessary to lower diastolic blood pressure to between 90 and 95 mm of mercury.

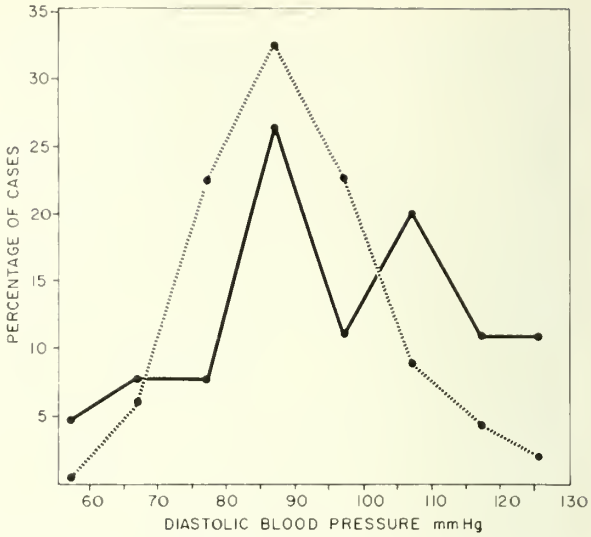

Figure 6.—Distribution of blood pressures in later life of multiparous women who had had eclampsia: Blood pressure distribution of 64 women who had had eclampsia in a pregnancy other than their first pregnancy (•—•), an average of 25 years after that pregnancy compared with 2,445 women matched for age and race from the Framingham study (•----•). (From Chesley et al.[13])

The last point I will consider is follow-up. We discussed the difficulty of diagnosing preeclampsia and that many of the women termed preeclamptic have evidence of another disease when renal biopsy specimens are studied. A woman who has preeclampsia in any pregnancy other than the first is clearly at risk of hypertension in later years (Figure 6). Chesley also followed women who were eclamptic in other than their first pregnancy.[13] There was an excess number of them with elevated blood pressures compared with the control women.

TABLE 7.—*Drugs for Treatment of Hypertensive Emergencies*

	Time Course of Action			*Dosage*			
Drug	*Onset (min)*	*Max. (min)*	*Duration (hr)*	*Intramuscular (mg)*	*Intravenous (mg)*	*Interval (hr)*	*Mechanism of Action*
Hydralazine	10-20	20-40	3-8	10-50	10-50	3-6	Direct dilation of arterioles
Diazoxide	1-2	2-3	4-12	..	300	3-10	Direct dilation of arterioles
	(min)	*(min)*	*(min)*	*Intravenous Solution (grams/l)*	*Intravenous Infusion Rate (mg/min)*		
Trimethaphan	1-2	2-5	10	2	1-15		Ganglionic blockade

Such patients deserve careful follow-up; however, one should keep in mind the fact that the blood pressure changes of preeclampsia do not resolve immediately. Many of the women normotensive at long-term follow-up in Chesley's study had still been hypertensive six weeks post partum. We usually reserve extensive evaluation for any woman who remains hypertensive three months post partum.

Conclusion

Preeclampsia-eclampsia is a fascinating disease. We do not know why it occurs. It changes a number of the physiological functions in ways that are dangerous to both the mother and her baby. We have been unsuccessful in attempting to improve fetal survival pharmacologically, probably because we start treatment after irreversible changes have occurred. At present, management remains a decision of whether the fetus is safest delivered or undelivered. Future progress in management of the disease should involve understanding what causes preeclampsia and developing simple tests that will allow us to recognize the disease before the clinical manifestations are present and before irreversible changes have occurred.

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Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Diseases Associated With High Levels of Immunoglobulin E

ALTHOUGH NOT measuring specific antibodies, the finding of an elevated serum level of total immunoglobulin E (IgE) of greater than 50 IU per ml may have diagnostic and therapeutic implications. For example, IgE levels greater than 400 IU per ml are found in more than 75 percent of patients with atopic dermatitis. The levels tend to be even higher with more severe disease or with coexistent asthma. Modestly elevated IgE levels have also been reported in conjunction with other dermatologic conditions such as neurodermatitis, contact dermatitis, dyshidrotic dermatitis, psoriasis, urticaria, alopecia areata and burns.

Although modestly elevated IgE levels are often found in patients with extrinsic asthma and are sometimes observed in patients with allergic rhinitis without asthma or eczema, levels found in these patients overlap those found in patients with nonatopic nasal and chest symptoms. Consequently, the total serum IgE level by itself does not reliably differentiate between allergic and nonallergic respiratory symptoms. Total serum IgE levels of less than 50 IU per ml do not exclude demonstrable specific IgE in specific patients with rhinitis, asthma or eczema.

Serum IgE levels greater than 500 IU per ml are characteristically found in patients with active helminthic infections involving organisms with a prominent tissue phase, such as schistosomiasis, filariasis, echinococcosis, strongyloidiasis, ascariasis, hookworm disease and trichinosis. IgE levels greater than 1,000 IU per ml are almost always found in patients with allergic bronchopulmonary aspergillosis, where the level of total serum IgE correlates with the activity of the disease. The IgE level may rise before a clinically defined exacerbation and subsequently fall with appropriate treatment.

Elevated serum IgE levels have also been reported in certain patients with Churg-Strauss syndrome, Wegener's granulomatosis, chronic eosinophilic pneumonia, Hodgkin's disease, sporadic bronchiolitis, childhood renal disease with proteinuria, and the hypereosinophilic syndrome. The significance of the elevated IgE levels in the development of these illnesses is largely unknown. However, in the hypereosinophilic syndrome, patients with elevated IgE levels tend to possess

fewer leukemic markers, are more responsive to corticosteroid therapy and have a better prognosis.

A syndrome has been recently defined which includes these characteristics: eczema, susceptibility to recurrent cutaneous and respiratory staphylococcal infections, a neutrophil chemotactic defect in autologous serum, variable T cell dysfunction, and substantially elevated levels of IgE (usually greater than 5,000 IU per ml). Elevated IgE levels have also been found occasionally in patients with other immunodeficiency disorders such as DiGeorge's syndrome, Nezelof's syndrome and chronic granulomatous disease The highest levels of circulating IgE are found, however, in those rare patients with IgE myeloma.

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Allergic Interstitial Nephritis

MORE THAN 300 cases of drug-induced allergic interstitial nephritis have been reported, constituting 3 percent to 8 percent of all cases of acute renal failure. The drug most often responsible for this disease is methicillin, although several other drugs have produced a similar allergic reaction.

The onset of symptoms is usually sudden, with evidence of renal impairment or frank renal failure occurring five days to five weeks after first administration of the drug. Oliguria with protein and cells in the urinary sediment is accompanied by rash, fever and arthralgias. Eosinophilia in blood and urine and increased levels of serum immunoglobulin E (IgE) are typical but are not found in all cases. The diagnosis is most often missed when the reaction complicates preexisting renal disease.

If the disease has been caused by administration of a drug, there is usually prompt remission of symptoms and signs when administration is discontinued. Often, however, the diagnosis is not suspected until after a renal biopsy has been done, which shows tubular interstitial edema and a patchy infiltrate of lymphocytes, plasma cells and eosinophils in the absence of significant glomerular or vascular disease. Recently, Linton and associates have shown that gallium citrate scintigraphy of the kidneys produces a substantial uptake of the isotope, which resolves in six weeks after the offending drug is withdrawn. The only other disease showing similar intense uptake is minimal change nephrotic syndrome, but usually this can be differentiated from allergic interstitial nephritis on clinical grounds. If this diagnostic technique is confirmed by further studies, it will lessen the need to do diagnostic renal biopsies.

The allergic nature of the disease is strongly suggested by the onset of fever, rash, joint symptoms and eosinophilia within days after the drug is given. Evidence suggests that several mechanisms may be operative. The eosinophilia and elevated IgE levels found in most cases suggest IgE-mediated disease, although wheal and erythema skin tests with the drugs in question are usually negative. The mononuclear cell infiltrate in the tubules is consistent with a cell-mediated process. The presence of immune complexes in renal tubules demonstrated by light or electron microscopy has been shown in only a few of the cases in which such complexes have been sought. In one patient, circulating antitubular basement membrane antibody was detected, suggesting that the drug might have triggered an autoimmune process in that case. No studies have been successful in producing the disease in animals so that information about immunopathogenesis must be inferred from further clinical studies.

Diagnosis requires a strong index of suspicion in any patient in whom renal insufficiency of sudden onset develops that cannot be explained on the basis of hypotension or sepsis. Although a renal biopsy can provide a definitive diagnosis, it is not necessary if clinical improvement occurs promptly after removal of the allergenic drug. Allergic interstitial nephritis should not be confused with analgesic nephropathy, a toxic reaction resulting in chronic tubular interstitial nephritis with tubular damage and fibrosis. This latter disease is associated with ingestion of high doses of analgesic drugs, most often phenacetin, and is found especially in drug abusers.

If allergic interstitial nephritis is diagnosed early, discontinuance of the drug will usually result in rapid recovery. Delay in diagnosis may necessitate hemodialysis because of severe renal damage. Reports of beneficial effects from corticosteroid therapy are difficult to evaluate because of inadequate controls, although such treatment is probably indicated if recovery is slow but uncom-

plicated by other preexisting renal disease. Readministration of the drug will invariably lead to recurrence of the problem and therefore must be avoided.

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Asthmogenic Drugs

CERTAIN DRUGS may adversely affect asthma by exacerbating a previously quiescent asthmatic condition or increasing the severity of established asthma.

The beta-adrenergic blocking drugs propranolol (Inderal) and nadolol (Corgard), when administered in high doses, exacerbate asthma and, therefore, probably should be contraindicated in moderate to severe cases of the disease. In response to beta-blocking therapy, mild coughing and wheezing may reappear in patients whose childhood asthma had been asymptomatic for many years. In mildly asthmatic patients who require these drugs, treatment should be initiated with low doses, such as 5 to 10 mg per day and then slowly increased while monitoring for bronchial obstruction. Metaprolol (Lo-Pressor) more selectively blocks beta-1 (cardiotropic) receptors than beta-2 (bronchodilator) receptors, so the drug has less potential for exacerbating asthma. However, it still must be used with caution in cases of moderate to severe asthma.

Aspirin and other nonsteroidal anti-inflammatory drugs, such as indomethacin (Indocin) and ibuprofen (Motrin), are capable of producing asthmatic attacks in certain patients, presumably by their inhibition of prostaglandin synthesis. Up to 4 percent of asthmatic patients and up to 2 percent of patients with rhinitis will experience asthma following the ingestion of these drugs. The percentage is even higher in patients with nasal polyps and asthma. "Triad asthma" involves a combination of bronchial asthma, nasal polyps and aspirin sensitivity. However, asthma and rhinitis commonly precede aspirin sensitivity, often by many years. Some aspirin-sensitive asthmatic patients react similarly to tartrazine (FD & C No. 5), a yellow coloring agent found in foods and also used in certain medications.

Paradoxical bronchospasm may occur after the inhalation of sympathomimetic aerosols, especially isoproterenol, when the drug has been overused. The mechanism for this phenomenon, however, is unknown. Therapeutic inhalation of sodium cromolyn (Intal) and acetylcysteine (Mucomyst) has been reported to cause bronchospasm by direct bronchial irritation.

Pituitary snuff, pancreatin, and *Bacillus subtilis* enzymes in detergents can cause immunoglobulin E-mediated allergic asthma.

In summary, a detailed drug history is critical to evaluation in newly asthmatic patients and in those with an exacerbation of chronic asthma.

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Why Nocturnal Asthma?

ASTHMA IS WORSE during the sleeping hours and its onset is often heralded by nocturnal coughing or wheezing. Factors attributed to this phenomenon of nocturnal asthma can be classified as mechanical (depressed pulmonary function in the supine position), allergic (bedroom dust, mite and feather allergens), psychological (frightening dreams) and biochemical (decreased serum cortisol levels).

Recent studies have shred fresh light on this subject. An inherent circadian variation in airway resistance is accentuated in patients with asthma. When such patients are subjected to hourly tests of pulmonary function, the best values are found during the afternoon hours and the worst between 10:00 PM and 8:00 AM. The differences are statistically significant and are present even when the patient feels free of symptoms. No correlation has been found between nocturnal asthma and dream states (as measured by rapid eye movement patterns) or nocturnal changes in circulating corticosteroid levels. Furthermore, a steady state infusion of hydrocortisone fails to ablate the circadian rhythm of airway caliber.

Barnes and associates have made some provocative comparisons between biochemical changes and nocturnal asthma. In five subjects with asthma they found decreased plasma epinephrine and cyclic adenosine monophosphate levels at 4:00 AM versus 4:00 PM. Plasma histamine

levels varied inversely, with the highest occurring during the early morning hours. Histamine levels did not rise comparably in subjects without asthma. Results of these studies imply that some breakdown in the homeostatic mechanism for controlling bronchomotor tone occurs in persons with asthma. Because antihistamines are not regularly effective against nocturnal asthma, other mediators of bronchoconstriction need to be determined before this aspect of asthma can be treated.

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Physical Urticarias: An Important Cause of Hives

THE PHYSICAL URTICARIAS are a group of diseases in which certain stimuli applied to the skin cause hives and, occasionally, respiratory symptoms. At least seven distinct forms of dermal stimuli can cause urticaria: heat, cold, sunlight, trauma, prolonged pressure, vibration and water. Heat, cold and solar urticaria, however, each exist in more than one form. Physical urticarias are usually acquired conditions, although there are two rare inherited forms—familial cold urticaria and vibratory urticaria. Generalized heat urticaria (cholinergic urticaria) and trauma urticaria (dermatographism) are relatively common, the latter occurring in 1 percent to 5 percent of the population. The mechanisms of most physical urticarias are poorly understood, although mast cell mediators are clearly involved in several of the forms. There is no association with other atopic disease, but immunoglobulin E antibodies may play a role in dermatographism and in some forms of acquired cold urticaria and solar urticaria.

The diagnosis of physical urticaria can usually be made by taking a careful history and carrying out appropriate challenge tests. Laboratory tests are of use only in excluding other conditions. Localized heat urticaria and primary acquired cold urticaria can be determined by exposure of an extremity to hot water or an ice cube, respectively. Dermatographism can be determined by stroking the chest or back with a blunt object, and aquagenic urticaria can be detected by application of distilled water to the skin. Solar urticaria can be induced by exposure to sunlight or ultraviolet light of specified wavelengths and vibratory urticaria by skin massage or vibration. Familial cold urticaria differs from acquired cold urticaria by a delayed response to cold (negative ice cube test), positive family history and systemic findings (leukocytosis, fever and arthralgias) at the time of the urticaria. Pressure urticaria usually occurs after prolonged pressure, and the wheals characteristically develop in association with tight clothing, especially at the waistline, shoulders, ankles or feet.

Cholinergic urticaria has a distinctive appearance of tiny wheals on a large erythematous base over the trunk, and it may become generalized with resulting bronchospasm. It is thought to be due to a dermal hypersensitivity to released acetylcholine and, thus, is provoked by exercise or factors which induce sweating (such as stress, emotion or heat). The intradermal test with methacholine has not been shown to be reliable for diagnosis of this disease.

Hypovolemic shock can sometimes occur with physical urticarias if the stimulus is intense or occurs over a large surface area. This is seen most often in acquired cold urticaria when there is a sudden, diffuse exposure to cold such as when one plunges into cold water. Patients with recurrent urticaria or unexplained anaphylaxis should be questioned about physical urticarias, and provocative testing should be done when appropriate.

Treatment of physical urticarias consists of avoidance of the causative physical stimulus, and administration of antihistamine drugs. Solar urticaria may benefit from appropriate-spectrum sunscreens. Steroids are rarely required.

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Respiratory Symptoms in Children Whose Parents Smoke

EPIDEMIOLOGICAL STUDIES have shown that upper and lower respiratory symptoms are more likely to occur in children whose parents smoke. Survey findings from the United States, Great Britain and Israel indicate that such symptoms occur most commonly if both parents smoke, less commonly

if one parent smokes, and least often if there is no smoking in the household. It was found that in families in which one parent smoked, only smoking by the mother produced a significant effect on the child. The child's symptoms were directly correlated wtih the number of cigarettes smoked by the mother as well as with maternal respiratory symptoms, but not with birth weight, birth order, social class or family size.

The symptom most commonly observed in infants less than 1 year of age, whose parents smoke, is cough, particularly during daytime hours, whereas older children generally have persistent wheezing in addition to coughing. Dyspnea and sputum production as well as upper respiratory symptoms that suggest recurrent colds or allergic rhinitis occur at all ages. Pulmonary function is inversely correlated with cigarette consumption by parents. There is no increased incidence of croup or bronchiolitis.

Although a familial genetic susceptibility to respiratory illness cannot be ruled out by such studies, it is more likely that the well-recognized irritant properties of cigarette smoke ("passive smoking") are the major factor in producing these ailments. Findings of several studies show a positive correlation of respiratory symptoms in infants and children with respiratory symptoms in their parents who smoke, which suggests cross-infection within the household as a possible mechanism. However, it is more likely that symptoms of both the children and adults are a reflection of the amount of exposure to smoke.

In the diagnosis of chronic coughing in infants and persistent wheezing in children, parental smoking must be considered to avoid possible misdiagnosis as recurrent colds, hay fever, asthma, bronchitis or pneumonia.

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EDITORIALS

There Will Be Changes Down the Road

EVENTS DURING the first months of the new federal administration suggest that there may be major changes in the ways America will address its problems during the remaining years of the 20th century. There seems to be substantial support for new approaches and the driving forces appear to be more economic than social or political. Quite simply it appears that we are running out of money and that printing more of it has made things worse rather than better. These realities suggest that much that is in place may either have to be abandoned or significantly altered, and that there will be a need for new approaches. It is not yet entirely clear exactly what needs to be done or exactly how it will be done, but for economic reasons, if for no other, there seems no doubt there will be changes down the road.

For nearly 50 years we have looked to government dollars and government regulations to solve many of our problems, and the public has supported many kinds of government intervention. But there now seems to be something of a voter consensus that the government is spending too much money and that this is part of the problem, and that in the process there has been too much government intrusion and too many government regulations attempting to control the personal and corporate lives of Americans. If the portents are correct, and if economic forces are to take precedence over the social and political, then it is likely that there will not be enough money to maintain the government and its beneficiaries in the manner to which they have come to expect and to be accustomed.

There is already clear evidence of an impending fiscal crisis which will affect health care as well as some other so-called entitlements, such as Social Security for the elderly and a right to public education for the young. The rhetoric is calling for a return to more personal responsibility, less fettered individual and private initiative and less restricted exploitation of national resources. If this rhetoric becomes national policy it will signal something of a turnabout, and the immediate and long-term effects on medicine and health care are really unpredictable but certain to be serious.

Philosophically, many if not most physicians (independent practitioners and independent persons that they are), will applaud this turnabout in national policy if it occurs. But the problems of substantially reduced government funding for health care, for health professional education and for research in health science will be severe. Government now funds approximately 40 percent of the health care now given in the United States and also has been heavily involved in supporting health professional education and biomedical research. And also of interest to physicians and the medical profession is the fact that we still and always will live in a closed biosphere and the fact that the ecological balance for health in this closed system is fragile, its natural resources are finite, its growing pollution is real, and that the law of entropy is immutable. Many physicians will be properly concerned that the license given to Biblical man to procreate and to exploit the Earth may no longer make as much sense as it did in Biblical times.

There will surely be changes down the road. If indeed there is to be a turnabout in national policy, what should be the stance of the medical profession with respect to health care, health professional education, research in biomedical science or health in a closed biosphere? How can this stance be made to influence or guide the real world of change? How can the responsibility for what needs to be done best be divided or shared between government and the private sector? One senses both an opportunity and an obligation for the medical profession to define its stance and to

work with others in the health field to help shape the changes which are sure to occur down the road. One looks to our leadership to see to it that we get our act together in timely fashion.

—MSMW

The Evaluation of Thromboembolic Diseases

What to Do Now That the Radioimmunoassay Has Arrived

ABOUT A DECADE AGO, an article entitled "The Diagnosis of Hyperparathyroidism (or What to Do until the Immunoassay Comes)" appeared in a leading clinical journal.[1] Bolstered by success with other radioimmunoassays, endocrinologists confidently predicted that a similar assay for parathyroid hormone would greatly simplify the diagnosis of hypercalcemia. We now know that this prediction did not prove entirely true and that considerable clinical acumen and extensive laboratory testing are still necessary to establish the correct diagnosis in a hypercalcemic patient. As we enter the second year of a new decade, radioimmunoassays are being developed for the study of patients with thromboembolic disorders and are predicted to have equal use.

Although thromboembolism occurs in a variety of clinical settings, it is facilitated by biochemical or cellular defects which permit activated products of coagulation to remain in the circulation, inducing a "hypercoagulable" state. Congenital absence of antithrombin, a plasma protein which inactivates serine proteases in the coagulation cascade, is a well-defined biochemical abnormality which is associated with a high incidence of thromboembolism. Undoubtedly, there are many other inherited and acquired abnormalities that create this hypercoagulable state, thereby predisposing patients to thromboembolism. For example, women who use oral contraceptives have a higher than expected incidence of thrombosis and vascular disease. It is clear that conventional coagulation tests, which are designed to measure failure of hemostasis and bleeding, are not able to predict thrombosis. Thus, a new generation of more appropriate tests has been developed to measure the events in blood coagulation that precede or accompany thrombus formation.[2] It is timely to review the limitations of these tests and to determine if they can detect patients with coagulation abnormalities before the onset of clinical thrombotic events.

ABBREVIATIONS USED IN TEXT

FPA = fibrinopeptide A
PF4 = platelet factor 4
βTG = β-thromboglobulin

A pioneering example of such a test is an immunoassay for fibrinopeptide A (FPA), one of two small peptides cleaved by thrombin during the conversion of fibrinogen to fibrin. FPA levels are elevated in patients with deep venous thrombosis and pulmonary embolism, but return to normal following administration of heparin.[3] Although FPA levels are clearly elevated in patients who have overt thrombosis, they have not yet been measured in such patients before thrombotic episodes. In addition, FPA levels are also elevated in patients with nonthrombotic inflammatory or autoimmune disorders such as systemic lupus erythematosus.

There are some technical problems which have limited the use of this assay. First, the available antisera cross-react extensively with intact fibrinogen so that all residual fibrinogen must be removed from test plasma before doing the assay. To be certain that the measured FPA levels reflect thrombin's action on fibrinogen, another immunoassay for a plasmin-generated fibrin fragment, such as fragment 1-42 of the β-chain of fibrinogen, must be done simultaneously.

More recently, assays have been developed for prothrombin-activation peptides and for the thrombin-antithrombin complexes that form in plasma after thrombin generation.[4] These assays do not require plasma processing because they use a highly purified antibody which recognizes new antigenic determinants on the protein fragment or complex, even in the presence of an excess of precursor molecules. These newer assays are promising but have not yet been tested in clinical situations.

Elsewhere in this issue, Wohl reviews the use of secreted platelet proteins to study thromboembolism and vascular disease. Plasma levels of two of these proteins, platelet factor 4 (PF4) and β-thromboglobulin (βTG), are elevated in a number of clinical situations. First, they are slightly higher than normal in patients with chronic vascular disease or diabetes mellitus, although there is considerable overlap within the

normal range. In addition, plasma levels of the two proteins are more strikingly elevated in patients with deep venous thrombosis, pulmonary embolism, arterial occlusion and myocardial infarction. Finally, PF4 and βTG are elevated in patients during episodes of spontaneous and exercise-induced myocardial ischemia and angina pectoris. Thus, an increased plasma level can signify platelet activation in chronic vascular disease or in acute ischemia and thrombosis. Although there is a close correlation, the tests do not distinguish between a primary and secondary platelet role in these diseases.

There are also some serious technical limitations to these assays. For example, it is not yet clear which of the protein measurements provides the best estimate of in vivo platelet activation. Because βTG is cleared and metabolized by the kidney, renal failure increases the plasma level of βTG without any activation of the coagulation system. PF4 might seem to be a superior marker because its plasma level is not influenced by renal function. However, it adheres to endothelial cells lining blood vessels and can be displaced by the administration of therapeutic concentrations of heparin.[5] While the presence of PF4 on vascular endothelium may have biological importance and may, in fact, modulate coagulation reactions, this interaction complicates the interpretation of plasma radioimmunoassays. To circumvent these problems, some investigators have suggested that both PF4 and βTG should be measured simultaneously and that a high ratio of βTG to PF4 would reflect in vivo release, whereas a ratio that approximates their content in platelets might represent release in vitro. Interestingly, in most clinical reports, plasma levels of both proteins rise in parallel.

Given these uncertainties, can such tests be applied clinically? If clinical application means ordering a battery of radioimmunoassays to diagnose early vascular disease or to predict impending thrombosis, the answer is probably no. However, techniques that can measure secreted platelet proteins and activation products or complexes formed during the coagulation process are valuable tools for clinical investigation. The assays should permit studies with human subjects that have previously been possible only with purified protein mixtures in vitro. For example, it should now be possible to determine (1) if coagulation reactions proceed in vivo by the pathways postulated from experiments in test tubes, (2) if there are patients in whom there is evidence for activation of coagulation before clinical thromboembolism (hypercoagulable state), (3) if the tests change in a predictable manner during acute thrombotic events and (4) if they can be used to monitor the efficacy of antithrombotic therapy.

It is hoped that the answers to these questions, as well as many other unforeseen ones, will soon become available. It may then be possible for clinicians to identify patients with a predisposition to thrombosis and then prescribe appropriate therapy. Radioimmunoassays of the coagulation system could then become as useful as their endocrine counterparts. However, only with more knowledge of the progression of such illnesses and the effect of therapy, both on the clinical outcome and the laboratory tests, will it be possible to predict the usefulness of these tests. For practicing physicians, the best approach, for the moment, may be to watch and wait. It should be remembered that, in medicine as in other human endeavors, "Time cools, time clarifies. . . ."[6]

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Adoption and Freedom of Information

ELSEWHERE IN THIS ISSUE Davis and Brown discuss changing attitudes and circumstances with respect to adoptions. Of particular interest is the fairly recent trend toward what might be called freedom of information among what is called the "adoption triangle"—that is, the true parents, the adopted child and the adoptive parents. A case is made that, for all concerned, knowing is better than not knowing and that physicians should do what they can to facilitate the exchange of information, whether in the care of their patients or by

acting as advocates in the community or for legislation.

In one sense this changing attitude may be viewed as a response to a loss which is shared by each part of the triangle as suggested by the authors, but it may also be an expression of a growing distrust of any practice which conceals information about a person from that person whether legally or otherwise. In any case it is always wise to ask why things got to be the way they are in the first place. There is always a reason, one which may or may not any longer be valid. This writer has a lurking feeling that a genuine maturity on the part of all the persons concerned may be necessary before all information can be exchanged without danger of harm to someone, and this may be a reason things got to be the way they are—that is, with safeguards. Genuine maturity is often not a characteristic of all the parties in the adoption triangle at the time of the adoption, and there is a primary responsibility to protect the interests of the adopted person, especially if a child.

—MSMW

Diet, Serum Cholesterol and Coronary Heart Disease

Has the Dilemma Been Resolved at Last?

THE DEBATE as to whether dietary quality and quantity is causally related to atherosclerosis has raged on for decades. As soon as a consensus appears to have been reached, foes of that consensus seem quick to publish recommendations based on the opposite conclusion. Most recently these have come from the skeptics (or nihilists, some would contend). First, an article by George Mann was published in the *New England Journal of Medicine*[1] entitled "Diet-Heart: End of an Era," and just last year the report of the Food and Nutrition Board of the National Research Council appeared.[2] Predictably, both of these reports, which concluded that insufficient evidence linking diet with coronary disease had been gathered on which to base recommendations for a change in national diet patterns, generated rebuttal which far outweighed the original reports.

Now that the brouhaha which followed the latter report has begun to abate (much of which took an unfortunate and unwarranted tone), we find the pendulum of fact and opinion swinging back toward that supported by the scientific establishment. That movement received substantial support in the recent report from the Chicago Western Electric Study,[3] which linked not only serum cholesterol with coronary risk in middle-aged men, a well-established association, but also, for the first time in an American multiethnic study, demonstrated a positive association between a score summarizing each participant's dietary intake of cholesterol and saturated and polyunsaturated fatty acids with their serum cholesterol level at the initial examination, a correlation between subsequent change in that score and change in serum cholesterol, and a significant relationship between the mean base-line diet score and the 19-year risk of death from coronary heart disease. The authors noted that conclusions from their study, if viewed in isolation, would be limited; when viewed in the context of the accumulated literature on the subject, however, their findings were interpreted to support the contention that dietary lipid composition affects not only the level of serum cholesterol but also, more important, the long-term risk of death from coronary heart disease in middle-aged American men.

A similar conclusion is reached in the article by Hulley and his co-workers, which appears elsewhere in this issue. As they have attempted with other controversial topics (for example, the relationship of serum triglycerides to coronary risk[4]), these authors have assessed the total literature to reach a strong conclusion, in this instance that "it is certain that dietary fats influence the level of serum cholesterol, and that it is highly likely that serum cholesterol is a cause of atherosclerosis and coronary heart disease." They then give broad guidelines for an approach to dietary intervention and estimate the resulting magnitude of reduction in coronary heart disease risk. (Parenthetically, experience and common sense challenge their calculated reduction in cholesterol. The total decrease of 140 mg per dl from all of the modifications illustrated is clearly not possible [and probably not desirable] in a person with a median cholesterol level of 213 mg per dl.) In short, despite their admission that the evidence linking dietary fats to coronary heart disease is largely circumstantial, they conclude that it is time to settle the matter and contend that their method of analysis has done just that.

But has it? We agree that more convincing findings are not likely to be forthcoming in the near future and that the essence of wisdom (and the

cornerstone of clinical judgment) is the ability to make correct decisions on the basis of inadequate evidence. However, we fear that the clamor for a simple answer to a complex question such as this risks uncritical acceptance and unwarranted, inappropriate application of the central conclusion of this analysis.

What, then, are the caveats and the exceptions to the general recommendation of this study? While all have been carefully acknowledged by the authors, they bear repeating here. First, there is a new, growing school of thinking that the lowest cholesterol may not be the most desirable cholesterol. Specifically, several (though not all) epidemiologic studies have demonstrated an inverse relationship between serum cholesterol and risk of cancer.[5] Whether this represents a true causal relationship or simply reflects the phenomenon of competing risks (that is, that age of death is relatively fixed and, hence, mortality from time-related processes such as cancer and coronary heart disease will be reciprocally related, a decrease in one being met with an increase in the other), a cholesterol-lowering diet is not indicated for all persons remains in question. It may be better, perhaps, for one's cholesterol to be nearer the "golden mean" than in the lowest percentile, despite the long-held contention that American cholesterol levels are generally far too high. Hence, the authors' recommendation that persons be allowed to individualize their diets on the basis of more informative labeling is particularly appropriate and laudable (though implying that knowledge of one's cholesterol level should be universal, a yet controversial issue). This is quite a different matter than endorsing a major, general change in the American diet, as recommended by the McGovern Committee.[6]

Second, well over half the American population (specifically, older men and women of all ages) cannot be included in the recommendations, because the strength of the relationship between serum cholesterol concentration and coronary risk declines to nonsignificance in old age (while the risks of any dietary intervention which jeopardizes adequate caloric intake increase), and studies of dietary intervention in women of any age have been notoriously uninformative, suggesting that the relative immunity to atherosclerosis enjoyed by (especially premenopausal) women may extend to the relationship between their dietary intake and their risk of coronary heart disease.

Third, those who have already experienced complications of atherosclerosis appear to gain little by altering their diets, their future course being predominantly determined by the severity of those complications.

Finally, let us turn to the real world of the principal readership of this journal and the critical dyad involved: the physician and the patient. Here the irony is clear, for those who would derive the greatest theoretical benefit from dietary change are the least likely to participate in such an encounter (since it is still axiomatic that the healthiest people are those who have never visited a doctor); conversely, those most likely to seek the counsel of a physician, namely women, the elderly, and those with symptomatic disease, are the least likely to derive benefit from dietary change. This frustrating situation and the eagerness of physicians to "do something" for their patients has led to much therapy which cannot be justified: unduly restrictive diets for the elderly, women and those with advanced atherosclerosis. Furthermore, even those cases of hypercholesterolemia that are detected while presymptomatic (often by selective screening of family members of patients with premature atherosclerosis) are likely to be a genetically determined form of hyperlipidemia. While the cholesterol level of such patients may decrease with dietary intervention, adjunctive drug treatment is almost always required to effect a substantial reduction, and management of the drug regimen will dominate the physician-patient encounter (often because the physician is ill-prepared or too impatient to give detailed dietary counsel).

Hence the authors' final recommendation will remain the essence of their paper for most practitioners; namely that "the decision to prescribe a fat-controlled diet . . . is a judgment that depends on the therapeutic philosophy of each clinician and on the particular needs of each patient." And we predict that it will ever be thus.

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CASE REPORTS

Refer to: Jaffe KM, Kraemer MJ, Robison MC: Hypernatremia in breast-fed newborns. West J Med 135:54-55, Jul 1981

Hypernatremia in Breast-Fed Newborns

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BREAST-FEEDING OFFERS several advantages to newborn infants.[1] Estimation of intake of breast milk in these infants, however, is difficult. This report describes an infant who had hypernatremia associated with inadequate breast-feeding and failure to thrive; four other cases with similar clinical courses have been reported.[2-4] To facilitate prevention and early recognition of this condition, the common features of these cases are reviewed.

Report of a Case

The infant, a 3,240-gram girl, was delivered at home by a midwife. It was the mother's first pregnancy. The infant was exclusively breast-fed every two to four hours and frequently fell asleep after five minutes of feeding. She cried very little when hungry and at 2 weeks of age had lost 855 grams (weight 2,385 grams). At 20 days she was first seen by a physician and admitted to hospital, weighing 2,200 grams. There was no history of vomiting, diarrhea or intake of other foods or medicines. At physical examination, the infant was emaciated but alert, sucked well and had signs of moderate dehydration (decreased skin turgor, depressed anterior fontanelle, sunken eyes, absence of tears and dry mucous membranes). Her length was 49.5 cm, occipital-frontal circumference 33.6 cm, pulse 108, blood pressure 90/50 mm of mercury, respiratory rate 24. Laboratory data included the following: serum sodium concentration 182, potassium 4.0, chloride 146 and bicarbonate 20 mEq per liter; blood urea nitrogen 94, serum creatinine 1.3 and serum glucose 108 mg per dl; hematocrit 69 percent. Urine had a specific gravity of 1.032, an osmolarity of 843 mOsm per liter and 2+ protein. Analysis of the mother's milk showed a sodium concentration of 39 mEq per liter on admission and 12 mEq per liter on discharge. There was no evidence of mastitis. The infant's hyperosmolarity was slowly corrected. When nursed she obtain only 20 to 30 ml of breast milk; thus, she was discharged on a schedule of breast-feeding with formula supplements averaging 145 ml per kg of body weight per day. Four days after discharge, her weight had increased 130 grams and the serum sodium concentration was 138 mEq per liter. A neurological examination showed no abnormalities.

Discussion

Hypernatremia in infancy can arise in a variety of clinical settings including central or nephrogenic diabetes insipidus, gastroenteritis, respiratory infections, salt intoxication and diminished fluid intake. The pathophysiological mechanisms are

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TABLE 1.—*Features of Five Cases of Hypernatremic Dehydration Associated With Inadequate Breast-Feeding*

	Clarke[2]	*Anand*[3]	*Anand*[3]	*Arboit*[4]	*Jaffe*
Age at presentation (days)	14	15	18	15	20
Supplemental feedings	None	None	None	None	None
Personality	"Sleepy"	"Sleepy"	NR	NR	"Sleepy"
Failure to thrive	+	+	+	+	+
Parity	1	1	NR	NR	1
Diminished milk production	NR (fed only 3×/day)	+	+	NR	+
Breast milk sodium concentration (mEq/l)	NR	31	74	104	39
Serum sodium concentration (mEq/l)	178	192	202	180	182

+ = present; NR = not reported

excessive free water loss, excessive sodium intake or diminished free water intake. The last mechanism seems the explanation in this and the four other reported cases.

All five infants shared common features: they were emaciated, less than 1 month of age and exclusively breast-fed—that is, with no water or formula supplementation (Table 1). Three of the infants were "sleepy," difficult to keep awake for feeding and content to starve uncomplainingly, a problem to which attention has recently been drawn.[5] One mother was noted to be upset by her difficulty in arousing her baby, but was reassured by family members that this was normal.[2] In the three cases where maternal parity was described, all mothers were primiparous. This suggests a lack of familiarity with normal newborn eating and sleeping patterns, and may explain why these mothers delayed seeking medical attention.

Although three of the mothers appeared to have diminished milk production, an expected finding in the face of diminished demand, only one was reported as perceiving her milk production to be inadequate.[3] Each had an unexplained increase in milk sodium concentration in comparison to a mean of 7 ± 2 mEq per liter reported by Macy[6] for women 15 days postpartum. In fact, these values were even high for women during the first five days postpartum when the mean sodium concentration is significantly higher (21 ± 5 mEq per liter).[7] This last association is an intriguing but unlikely explanation for the hypernatremia. The infants' diminished intake, suggested by the emaciation and degree of dehydration, makes it improbable that they ingested a high amount of sodium. The cause of the increased milk sodium concentration remains uncertain.

Without any evidence of excessive free water loss, the explanation for the hypernatremia in these five infants is diminished free water intake. The combination of large insensible water losses and diminished renal concentrating capacity makes newborn infants susceptible to water depletion. Even nursing infants who have low obligatory urinary water loss (because of breast milk's low solute content) can become water depleted when intake of breast milk decreases to the extent that the renal concentrating capacity is exceeded.

Comment

The five cases of hypernatremia in breast-fed newborns emphasize the importance of frequent follow-up of newborn infants. Careful attention must be paid to the adequacy of their weight gain. Although most babies cry when they are hungry, health professionals who care for newborns must be aware that otherwise normal babies may be content to nurse infrequently, and thereby fail to thrive and, in this context, become hypernatremic. With adequate instruction of mothers and proper care of their breast-fed infants, this potentially damaging condition[8] can be prevented.

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Bile Duct Stricture Shown During Transhepatic Cholangiography by Use of Cholecystokinin

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THE HORMONE cholecystokinin (CCK) has been used to show gallbladder contraction during cholecystography (following oral ingestion of contrast material). We report the case of a patient with a stricture of the common bile duct in whom CCK was used during transhepatic cholangiography

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ABBREVIATIONS USED IN TEXT
CCK = cholecystokinin
THC = transhepatic cholangiography

(THC) to cause gallbladder contraction, which facilitated the outline of the biliary stricture.

Report of a Case

A 40-year-old black man was admitted to the Liver Unit, Rancho Los Amigos Hospital in December 1979 because of recurrence of abdominal pain and jaundice. The patient had been alcoholic for ten years and had had multiple bouts of acute pancreatitis. He was first noted to be jaundiced in October 1979 following one of these episodes. On that occasion, an endoscopic retrograde cholangiopancreatogram showed changes in the pancreatic ducts consistent with chronic pancreatitis and a stricture in the intrapancreatic portion of the common bile duct. The jaundice resolved and the patient was temporarily lost to follow-up after discharge from the hospital. On admission to hospital on December 20, he presented with a similar history and stated that he had continued to take alcohol. The only abnormalities found on physical examination were scleral icterus and a liver edge that was just palpable in the right costal margin on deep inspiration. Laboratory test results included a serum albumin of 3.9 grams per dl, serum alkaline phosphatase 11.3 Bessey-Lowry units (normal range 0.8 to 2.3), total bilirubin 10.6 grams per dl, serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) 524 IU per liter, serum alanine aminotransferase (serum glutamic pyruvic transaminase) 224 IU per liter, prothrombin time 100 percent of control value, serum amylase 1,870 U per ml, hemoglobin 15.2 grams per dl and leukocyte count 10,500 per cu mm, with a normal differential count.

An ultrasound examination of the liver and gallbladder showed evidence of dilated intrahepatic and extrahepatic ducts but no evidence of cholelithiasis. A percutaneous THC was done, using a 23-gauge Chiba needle. The needle first entered a right-sided bile duct. After aspirating about 30 ml of green bile, contrast material was injected. The right intrahepatic ducts were not dilated, but the left-sided ducts as well as the main hepatic and proximal common bile ducts were dilated. The gallbladder was considerably elongated and filled with contrast material. However, there was an abrupt stop of the contrast material at the level of the suprapancreatic portion of the common bile duct, and a nipple-like deformity was noted (Figure 1). For ten minutes repeated attempts were made to place the patient in the upright position; however, no dye passed beyond the suprapancreatic portion of the common bile duct.

Figure 1.—Film of contrast material in bile duct and gallbladder (GB) before administration of cholecystokinin, showing what appears to be complete obstruction of the common bile duct (CB). This film was taken while the patient was in the upright position, after removal of the needle.

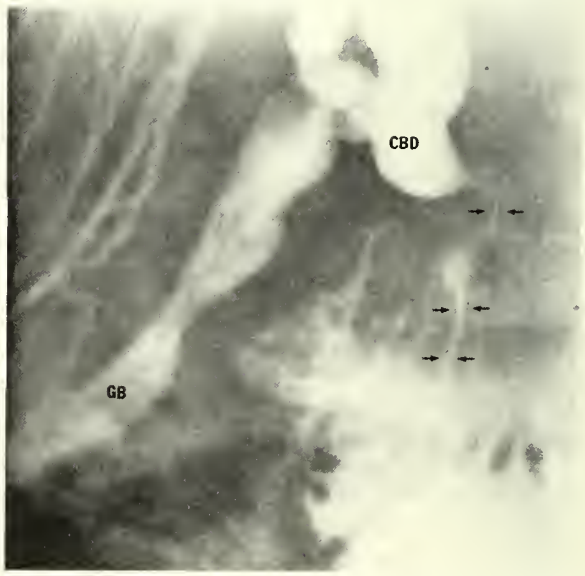

Figure 2.—Film taken three minutes after administration of cholecystokinin, showing substantial contraction of the gallbadder (GB). The contrast material outlines the stricture of the common bile duct (CBD) (arrows), with spillage into the duodenum.

Within two minutes following intravenous injection of 1.4 μg of Kinevac (an active synthetic C-terminal octapeptide of CCK), there was substantial contraction of the gallbladder with passage of the dye into the duodenum and outlining of the strictured area of the common bile duct (Figure 2). There were no gallstones in the entire biliary system.

The patient tolerated the procedure with only a short episode of cramping abdominal pain. All laboratory test results returned to normal ranges within three weeks and the patient was discharged from the hospital as he declined any therapy for his bile duct problem.

Discussion

Transhepatic cholangiography is a useful procedure in the investigation of obstructive jaundice. The technique we used was similar to that described by Okuda and co-workers,[1] in which a 23-gauge Chiba needle is inserted percutaneously into an intrahepatic bile duct from an entry point in the right flank. In incomplete obstruction of the biliary system, placing the patient in the upright position often allows the contrast material to pass the obstruction and reach the small intestine. In this case, however, such a maneuver was unsuccessful. Therefore, CCK was used to cause contraction of the contrast-filled gallbladder which it was hoped would force the contrast material through the obstruction and allow it to reach the small intestine, thereby outlining the stricture. As shown in Figures 1 and 2, CCK caused a very prompt contraction and the contrast material clearly outlined the stricture. CCK has been used in radiology for many years to investigate gallbladder contraction during cholecystography,[2] but we are unaware of its use as described above. CCK may be a safe and useful adjunct in carrying out THC in selected circumstances. It can be useful in outlining a stricture in the common bile duct when the obstruction is incomplete and is below the entry of the cystic duct and when there are no small stones in the gallbladder that might be forced into the common bile duct. Presumably, this technique is of use only in gallbladders which are capable of contraction, as CCK does not appear to have an action on the bile duct.[3]

Summary

A stricture of the common bile duct developed in a 40-year-old man due to recurrent chronic alcoholic pancreatitis. The stricture was able to be visualized during transhepatic cholangiography following injection of cholecystokinin, which caused contraction of the gallbladder (that was filled with contrast material) and forced the material through the strictured area.

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Adenocarcinoma Arising in Gastric Heterotopic Pancreas

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HETEROTOPIC PANCREATIC TISSUE may be found anywhere from the distal end of the esophagus to the colon in the alimentary canal. Its location outside the alimentary canal also has been reported.[1-4] Symptoms associated with heterotopic pancreas are uncommon, but when present are usually associated with a gastric site. In this location, symptoms resemble those of peptic ulcer or pyloric obstruction.[2,5,7-10] The spectrum of pathological changes characteristic of the main gland including, rarely, pancreatic cancer is shared by heterotopic pancreas.[2,3,6,11-21] This paper reports a case of gastric heterotopic pancreas giving rise to a nonislet cell pancreatic carcinoma. A discussion of other reported cases of pancreatic cancer thought to have arisen from gastric heterotopic pancreas is given and a plan for surgical management is recommended.

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Report of a Case

A 58-year-old man entered the Martinez Veterans Administration Medical Center (MVAMC) in March 1979 with a six-month history of an enlarging mass located in the inferior aspect of an old midline incision, a 25-pound weight loss and periodic epigastric pain and vomiting.

In October 1972 the patient had been admitted to another hospital with an ulcerating obstructing tumor of the pylorus. At that time a subtotal gastric resection for a localized tumor of the pylorus was done; there was no evidence of lymph node metastasis. Heterotopic pancreas was noted in the resected specimen. Clinically, the patient had done well until his present illness.

On March 23, 1979, a wide excision of the anterior abdominal wall around the biopsy site was carried out. No gross tumor was detected at celiotomy, except for a 1-cm nodule in the right anterior pelvis, which was excised. On microscopic examination, biopsy specimens of the abdominal wall and pelvic nodule were identical to that of the excisional biopsy. A review of the slides of the pyloric tumor excised in 1972 showed the previously reported benign heterotopic pancreas, but, in addition, adenocarcinoma similar to the present specimen was seen in some sections.

Figure 1.—Low magnification of section of nodule showing ductal structures surrounded by smooth muscle cells (tumor in stomach, 1972).

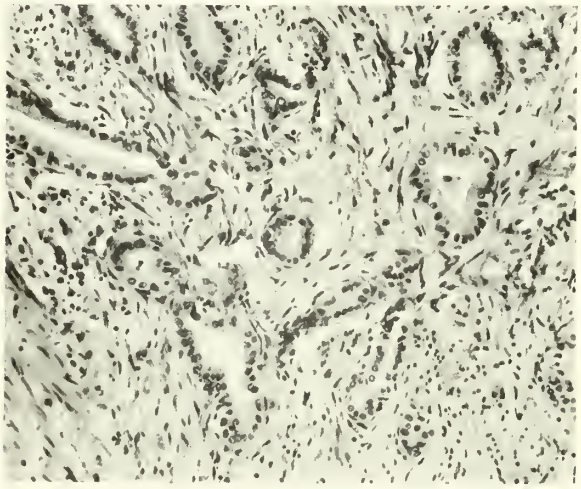

Figure 2.—An area of infiltrating malignant glands (from same tumor as in Figure 1).

In October 1979 the patient was readmitted to the MVAMC because of pneumonia, discharged uneventfully, and then admitted to a hospital in Texas, again because of pneumonia. At that time an obstruction of the small bowel was reported to have developed, which required celiotomy. Multiple peritoneal studding with metastatic pancreatic adenocarcinoma was discovered during the operation.

Pathological Findings

A portion of the stomach removed for gastric outlet obstruction (October 1972) showed a mass 2.3 cm in diameter in the pylorus. This firm rubbery mass was located in the muscularis propria, and the cut surface showed multiple tiny cystic spaces.

On microscopic examination of the nodule, small cysts or dilated ducts of pancreatic type cells surrounded by smooth muscle cells were found, which were interpreted as adenomyoma (Figure 1). No exocrine acini or islets of Langerhans were seen. Other areas showed small infiltrating glands composed of malignant nuclei (adenocarcinoma) (Figure 2), with desmoplastic reaction.

Sections of the recurrent tumor (March 1979) showed similar ductal structures (Figure 3) as in the original mass, as well as areas with infiltrating duct carcinoma and desmoplasia (Figure 4).

Discussion and Review of Literature

Shultz was first to describe heterotopic pancreas in 1727, although histological data were not available until the report by Klob in 1859, in which the latter presented two cases of heterotopic pancreas, one of which was located in the stomach.[3] While heterotopic pancreas may be found throughout the gastrointestinal tract and abdomen, between 25 percent and 40 percent of lesions are located in the stomach, especially the antrum. The majority of lesions are asymptomatic. Heterotopic pancreas is discovered in approximately 1 in

500 operations involving the upper abdomen, and it is identified in 0.55 percent to 13.7 percent of autopsy series.[3,22]

Embryologic Aspects

In a 6-week embryo, the pancreas arises as two separate outpouchings of the endodermal epithelium of the duodenum. The ventral pancreas divides into a left and right bud, and only the right bud persists to eventually migrate into the dorsal mesentery to lie below and behind the dorsal pancreas. The parenchyme and ductal structures of the dorsal and ventral pancreas fuse. The ventral pancreatic duct and the distal part of the dorsal pancreatic duct combine to form the main pancreatic duct of Wirsung. The parenchyma gives rise to the islets in the third fetal week.

Various theories have been offered to describe defects in this embryology that might account for heterotopic differentiation separate from the main gland. Small buds of pancreatic parenchyma and rudimentary ducts may be retained by the bowel wall and carried a variable distance from the main gland by the normal growth of the alimentary tract.[3] Metaplastic changes in gut endoderm may occur during prenatal life, as well as atavism, in which there is reversion to lower life forms which have pancreatic tissue in other locations.[4,10]

Morphological and Histological Aspects

The typical appearance of lesions of gastric heterotopic pancreas as supported by endoscopic observation is that of polypoid submucosal growths occasionally displaying nipple-like protuberances of the mucosa that smooth out with the gastric peristaltic wave. The tissue appears as discrete yellowish-gray nodules with well-defined lobules of acinar tissue that may be replete with islands of Langerhans as well as exocrine glands. These nodules range in size from 1 mm to 5 cm. The lesions in the stomach are usually larger than in other sites, averaging 2.4 cm[2,16] and are situated in the submucosa or muscularis. There is usually a duct system that communicates with the gastric mucosa.

Natural History

Heterotopic pancreas is subject to all the diseases of the main gland. This is particularly important when the location is in the stomach because the lesions may ulcerate and cause substantial gastric bleeding[7] and enlarge to cause obstruction in their predominantly pyloric site.[3] Of the cases of gastric heterotopic pancreas that are diagnosed and symptomatic, it is known that approximately 10 percent are ulcerated[16] and nearly 25 percent are obstructive to the gastric outlet.[16,23] These figures have no predictive value as to the course of nonpathological gastric heterotopic pancreas since the pathological changes of lesions that are undiagnosed are not known.

Malignant change in heterotopic pancreas is rare. The well-differentiated cell structure and predominantly submucosal location of gastric heterotopic pancreas make it an infertile soil for neoplastic transformation. It is not clear why this lesion, if antenatal in development, occurring in gastric or other locations, and having similar his-

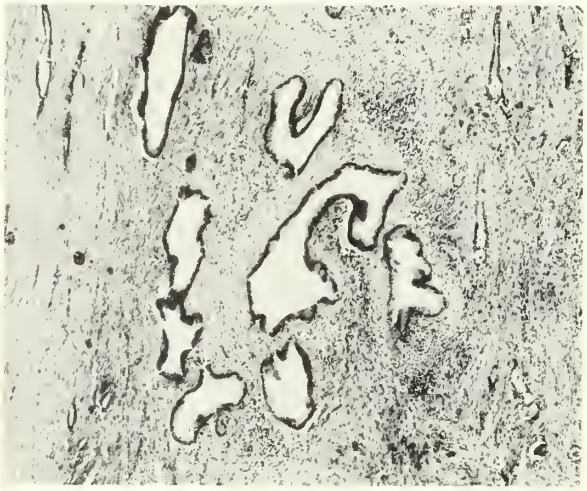

Figure 3.—Section of recurrent tumor in abdominal wall (excised in March 1979), showing benign-appearing ductal structures.

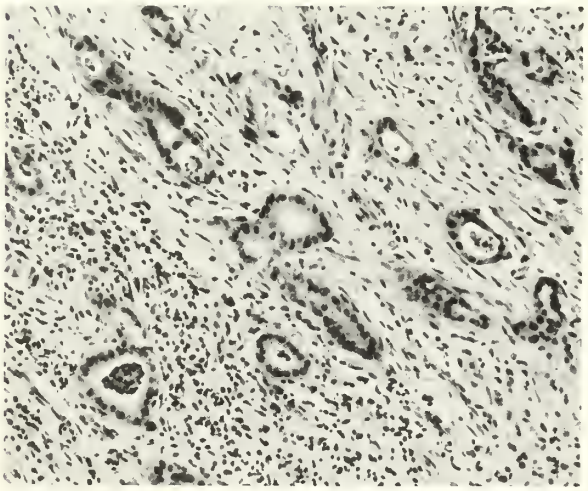

Figure 4.—Section of infiltrating ductal carcinoma in recurrent tumor of the abdominal wall (same tumor as in Figure 3).

tological features, may exhibit no behavior in some patients, and undergo pathological change, including neoplastic transformation, in others.

The clinical course of patients with carcinoma arising from gastric heterotopic pancreas seems to parallel that of primary gastric carcinoma as opposed to that of primary pancreatic carcinoma, from which there are very few five-year survivors.[24-28] The five-year survival of patients with gastric carcinoma is low but not as hopeless as in cases of pancreatic cancer. Also, operations in selected cases do provide a 30.2 percent five-year survival rate.[24] However, the overall five-year survival of patients with either gastric or pancreatic carcinoma continues to be unsatisfactory.

The occurrence of metastatic disease soon after primary surgical resection signals a poor prognosis. The finding of recurrent metastatic tumor in the case reported by Goldfarb[6] six years after primary resection and the detection of tumor in the abdominal wall seven years after resection in our case, indicates a relatively benign course for some carcinomas arising in gastric heterotopic pancreas. It is possible but unlikely that in our patient, benign heterotopic tissue was tracked into the abdominal incision and pelvis, and eventually degenerated into malignancy. Growth of benign tissue that is tracked into an abdominal incision has been described.[29,30]

Gastric Heterotopic Pancreas and Carcinoma

Cases of gastric carcinoma presumed to arise from heterotopic pancreatic tissue are rare. Precise histological description of the tumor and surrounding or contiguous heterotopic pancreas is not presented in most reports.[15] A satisfactory explanation as to the origin of gastric tumors said to have arisen truly in heterotopic pancreatic tissue is lacking in the literature.

It is known that heterotopic pancreatic tissue may not have all the typical pancreatic elements. Moreover, pancreatic carcinoma can arise only from elements of the pancreatic ductal system or from acinar type cells resembling the parenchyma of the pancreas. The origin of carcinoma arising in heterotopic pancreas, therefore, may be confused if all the usual elements characteristic of the pancreas are not identified.

In 1904 Pforringer[19] first reported on the association of gastric carcinoma with heterotopic pancreas. He described a solid gastric carcinoma which appeared to arise submucosally. Adjacent to this mass in the duodenal wall was a tumor composed of accessory pancreatic tissue. Continuity between the two lesions was not demonstrated. In 1908 Branham[12] published a case of nonislet cell carcinoma and heterotopic pancreas arising submucosally in an obstructing pyloric tumor. The structure of the heterotopic pancreas was atypical compared with normal pancreas and different from the carcinomatous tissue.

In a number of the reports in the literature there is little objective evidence to support the conclusion that neoplasia arose from the heterotopic tissue. Askanazy[11] in 1923 described a solid submucosal gastric carcinoma, but no heterotopic pancreatic tissue could be identified. In 1923 Nicholson[18] reported on a large gastric tumor discovered at necropsy which was composed entirely of pancreatic epithelial carcinoma. The pancreas showed no new growth. There were no signs of accessory pancreas in the report by Borrmann[15] in 1926, when he suggested that a solid gastric carcinoma had developed from pancreatic tissue. A similar problem exists with the report by May[17] in 1937. While in 1958 Martinez and co-workers[16] reported that 2 of 51 cases of gastric heterotopic pancreas were associated with carcinoma, they present no description of the neoplasm and pancreatic tissue. Barbosa and colleagues[2] in 1946 reported on a carcinomatous gastric ulcer overlying a mass of heterotopic pancreas, again, without histological description.

Only five articles on this subject have appeared in the last 20 years. Horanyi and Buday[14] diagnosed a heterotopic adenomyosis that became malignant at the site of a gastroenteroanastomosis that had been done 40 years previously. Jarvi and Lauren[15] reported two cases and challenged a number of the earlier cases of neoplasia thought to have arisen from gastric heterotopic pancreas. They presented histopathological data that supported a theory that gastric glandular tumors said to have arisen in pancreatic heterotopia may have been confused with gastric tumors that had ductal and acinar elements similar to tissue seen in salivary glands or the pancreas. Goldfarb[6] in 1962 and Vrabeviski[20] in 1967 reported on gastric carcinomas in which heterotopic pancreatic tissue and the neoplasm both showed typical pancreatic glandular and islet elements. The most recent examination of the subject of cancer of the stomach arising from heterotopic pancreas was by Debray and co-workers[13] in 1978.

Diagnosis

There is no specific symptom complex with lesions of gastric heterotopic pancreas. Symptoms have been held responsible for nearly any clinical picture that might generate an investigation of the upper alimentary tract. Upper abdominal pain is present in 55 percent to 75 percent of patients.[16,22] The pain may occur with the ingestion of meals, postprandially or in a rhythmic pattern like an ulcer. Nausea and vomiting, eructation, hematemesis, hematochezia or melena may be present. Cachectic patients with a gastric tumor may be suffering from the sequelae of pyloric obstruction, but might be harboring a carcinoma at that site.

Radiography and endoscopy can characterize the lesions of gastric heterotopic pancreas in most cases.[31-34] The mass of heterotopic pancreas is either broad based and smooth, characteristic of an extramucosal intramural tumor, sessile with a narrow base like that of a polyp, or umbilicated, resembling a healing ulcer or ulcerated neoplasm. Barium may be seen to fill a 1- to 2-mm niche in the center of the lesion which marks the site where the heterotopic excretory ducts empty into the stomach. Because on radiography some of the lesions appear large and ulcerated like malignant lesions, polypoid-like gastric adenomatous polyps or, occasionally, similar to submucosal myomatous gastric tumors, endoscopic biopsy specimens and washings may clarify the diagnosis.[33,35,36] When the lesions are first detected during an operation they should be excised and frozen sections obtained.

Management

Most cases of gastric heterotopic pancreas are discovered (1) as an incidental finding on upper gastrointestinal series, (2) at operation, coincidental to some other pathological condition contributing to the surgical indications or (3) at autopsy. Thus, this entity is usually unrecognized clinically and its course is generally benign. If the tumor has been recognized preoperatively on a gastrointestinal series or during endoscopy, biopsy specimens and washings should be obtained to establish the diagnosis. Should it be impossible to obtain histological confirmation of the nature of the lesion, it is not always necessary to operate. Asymptomatic lesions of less than 2 cm can be followed without specific therapy. The exception is in a patient with a lesion of 2 to 3 cm or more in diameter. The 2- to 3-cm tumor detected in our patient in 1972 was smaller than that usually associated with carcinoma for heterotopic pancreas of gastric location. However, the clinical presentation consisting of weight loss, nausea and vomiting, and a gastrointestinal series that showed an ulcerating obstructing lesion, was more compatible with malignancy. It appears prudent to treat all patients with 3-cm lesions even when asymptomatic. The occurrence of symptoms, most notably obstruction or bleeding, with lesions under 2 to 3 cm indicates a progression in size of the lesion or ulceration, and perhaps malignancy. The recommended treatment of these lesions depending on location is usually excision by subtotal gastric resection. Local resection should be reserved for small lesions 2 cm or less in diameter and without gross evidence of malignancy.[16,37] At operation biopsies should always be done.

Summary

A case of adenocarcinoma arising in gastric heterotopic pancreas is presented. In reviewing the literature, 15 reports of this entity were found, of which perhaps half gave histological evidence to support the tenet that the carcinoma did arise directly from the heterotopic tissue. All lesions of gastric heterotopic pancreas that are symptomatic, particularly with bleeding or obstruction, or are found to be 3 cm or more in size, regardless of the presence of symptoms, should be treated with subtotal gastric resection. The clinical course of cases of carcinoma within gastric heterotopic pancreas appears to parallel that of primary gastric cancer, and, therefore, the management should be the same. Late recurrence is likely even when the lesion is well-differentiated and confined to the stomach wall.

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Reflex Sympathetic Dystrophy of the Lower Extremity

A Complication of Herpes Zoster With Dramatic Response to Propranolol

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REFLEX SYMPATHETIC DYSTROPHY (RSD) is a symptom complex consisting of pain, swelling, trophic skin changes and vasomotor instability in a distal extremity in response to an injury. The distal extremities, most often hands or feet, are affected, but involvement of sites such as knees, hips and zonal portions of the femoral head have also been reported.[1-7] The most common precipitating causes are trauma, either fracture or soft tissue injury, myocardial infarction, cervical spine or spinal cord disorders, osteoarthritis, cerebrovascular accident, malignancy, infection and drugs. However, as many as a third of cases have no antecedent event.[4,7]

First recognized as a distinct entity during the American Civil War, reflex sympathetic dystrophy was originally named causalgia (from the Greek words for heat and pain) because of its characteristic burning pain.[8,9] Since then, several different descriptive terms, such as shoulder-hand syndrome, Sudeck's atrophy, posttraumatic osteoporosis and postinfarction sclerodactyly, have been used synonymously with this rare disorder.

Herpes zoster infection has been associated with the development of RSD in an upper extremity. Ketz and Schliack[10] reported RSD of the shoulder and hand secondary to herpes zoster infection of the fifth and sixth cervical nerve roots. To our knowledge, however, this is the first published case of reflex sympathetic dystrophy of the ankle and foot of the same leg secondary to painful herpes zoster infection of the first sacral dermatome. Also, a dramatic response to propranolol was noted in this patient after failure of conventional RSD therapy.

Report of a Case

A 72-year-old man had a six-week history of painful swelling of the left ankle and foot. The

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Submitted, revised, August 15, 1980.

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pain was constant, dull and exacerbated by movement of the true ankle and metatarsal phalangeal joints and weight bearing. The patient had had herpes zoster infection, involving the first sacral dermatome on the left, which had resolved four weeks before onset of these symptoms.

The patient was treated with intramuscular injections of dexamethasone, acetaminophen with codeine, and nonsteroidal anti-inflammatory drugs, with no relief of symptoms. Roentgenograms of the foot at that time showed no abnormalities.

Past medical history included a myocardial infarction in 1976 and a cerebrovascular accident in 1978, with residual right hemiplegia.

On admission of the patient to this hospital, a physical examination showed no abnormalities of the head, ears, eyes, nose or throat. Chest was clear to auscultation and abdomen was soft and nontender. There was no hepatosplenomegaly. The skin over the left calf had many 3- to 6-mm hyperpigmented areas. Nonpitting edema involved the left foot and ankle to midcalf. The skin overlying the nonpitting edema was very tender to palpation and cool to the examiner's touch (Figure 1). Range of motion of the left ankle was normal but painful. There was mild muscle weakness on the right. Deep tendon reflexes were symmetric with no pathological reflexes. Dorsalis pedis pulses were absent bilaterally; all other pulses were palpable. Vibratory sensation and light touch were intact bilaterally.

Results of laboratory tests included the following: hemoglobin 14.8 grams per dl and hematocrit 44.3 percent, with a leukocyte count of 7,000 per cu mm. Serum alkaline phosphatase, albumin, calcium, phosphorus, uric acid, glucose and blood urea nitrogen values were within normal limits. Westergren sedimentation rate was 8 mm per hour. Tests for rheumatoid factor, antinuclear antibody, hepatitis B antigen and HLA-B27 were negative.

Roentgenograms of the left foot and ankle initially showed no bony abnormality (Figure 2). However, roentgenograms of the left foot taken four weeks later showed patchy osteopenia involv-

Figure 1.—Nonpitting edema of the left foot and ankle is contrasted with normal right foot.

Figure 2.—Roentgenogram of left foot at onset of symptoms showing no bony abnormality.

ing the metatarsal phalangeal joints, consistent with the diagnosis of reflex sympathetic dystrophy (Figure 3). No erosive changes were noted. A bone scan with technetium 99m diphosphonate showed increased uptake in the left ankle and foot (Figure 4).

An aggressive physical therapy program was begun as well as a regimen of salicylate and nonsteroidal medications. After six weeks of intensive therapy there was no change in the patient's signs or symptoms.

Because there was no history of myocardial dysfunction, asthma or diabetes mellitus, oral propranolol therapy, 160 mg per day in four divided doses, was tried. Follow-up after a week showed a 50 percent decrease in swelling of the left lower extremity and the patient was able to bear weight. Within four weeks, the swelling, hyperesthesia and pain had completely resolved (Figure 5). Propranolol therapy was gradually tapered off during the next eight weeks. Repeat roentgenogram was

Figure 3.—Roentgenogram of left foot taken six weeks after symptoms appeared shows patchy osteopenia mainly involving distal metatarsal and interphalangeal bones.

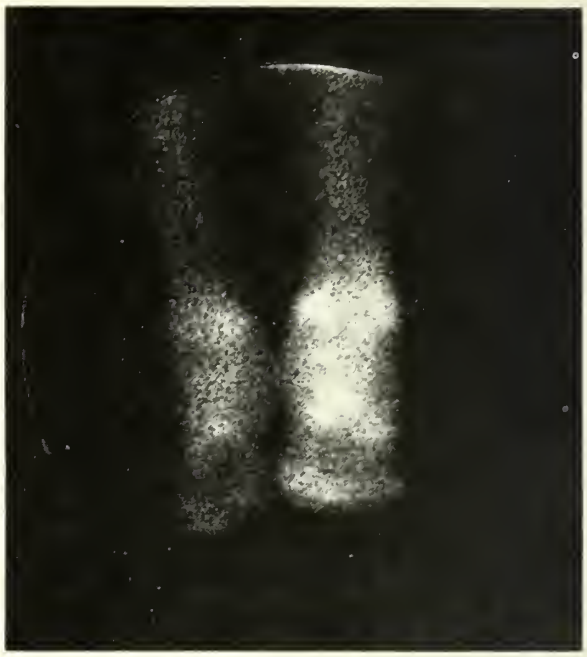

Figure 4.—Bone scintigram shows increased radioisotope uptake around the left ankle and metatarsal joints. Note the soft tissue swelling of left foot.

Figure 5.—View of left foot and ankle after four weeks of propranolol therapy, showing resolution of swelling.

Figure 6.—Repeat bone scintigram after 10 weeks of propranolol therapy shows equal radioisotope uptake in both ankles and feet.

unchanged (patchy osteopenia still present); however, a repeat bone scan showed equal uptake of radioisotope in both ankles and feet (Figure 6). Eight months later, he was still asymptomatic.

Discussion

This case illustrates the salient clinical features of reflex sympathetic dystrophy. RSD is much more common in older adults, probably because of a predilection of the precipitating causes for this age group. Surprisingly, a substantial number of these patients have a history of psychiatric disturbance before the onset of illness, suggesting that a certain emotional profile may be a predisposing factor.[2,6]

The pain is described as burning in nature and most severe in the periarticular tissues. Swelling of the involved extremity can be pitting or nonpitting, as in this case, but localized to the painful periarticular area. Vasodilatation or vasoconstriction is noted. Sometimes Raynaud's phenomenon or hyperhidrosis is observed, but most often the involved extremity appears pale and cool to the examiner's touch.

Roentgenograms are helpful in making a diagnosis. Findings may be normal at onset but within a few weeks, characteristically, they show soft tissue swelling and patchy osteopenia that is juxta-articular.[1,11,12] Figure 3 shows the mottled appearance of the bone that developed around the metatarsal joints in the patient's involved foot, contrasted with the earlier, normal appearing roentgenogram (Figure 2).

Other roentgenographic changes include diffuse osteopenia with a "ground glass" appearance, cortical bone resorption and juxta-articular subchondral erosions, usually appearing late in the course of the disease.[1,11] The erosive changes are believed to result from hypervascularity and increased osteoclastic bone resorption.[1]

Hypervascularity of the involved extremity accounts for the increased activity noted on both bone and joint scintigrams.[1,7,11] A bone scintigram in this patient showed increased uptake in the affected ankle (Figure 4).

The mechanism of RSD remains unknown. Turek[13] proposed that an irritative focus provokes continuous vasospasm of the terminal arteriole. Distention of capillaries and venules occurs and blood stasis results in the formation of edema. The local acidosis stimulates osteoclasts to resorb bone.

Melzak and Wall have suggested that sympathetic impulses feed the same receptor centers as the small fibers mediating pain transmission and large fibers that inhibit it, and are influenced by higher perceptual and cognitive processes.[14] Thus, RSD may result from stimulation of efferent sympathetic fibers by afferent pain impulses, cognitive or perceptual influences or direct irritation of the receptor centers.

Mobilization and aggressive physical therapy remain the mainstays of treatment. Anti-inflammatory drugs, high doses of corticosteroids given orally, sympathectomy and manipulation under general anesthesia all have been reported successful in selected patients.[2-6,15-17] Intravenous administration of guanethidine to the affected limb has been noted to achieve rapid reduction of pain and edema.[18,19]

Propranolol therapy was tried in this patient after conventional treatment failed, based on Simson's report[20] of dramatic improvement with propranolol in two cases of RSD. The prompt resolution of his signs and symptoms after the initiation of propranolol suggested that a spontaneous remission was unlikely.

The mechanism of action of propranolol in RSD is unknown. Propranolol is a β-adrenergic receptor blocker. It is capable of blocking the effects of catecholamines and sympathetic nerve stimulation on heart rate, cardiac output and contractility. Recent studies have shown administration of pro-

pranolol reduces the response to sympathetic nerve stimulation in human peripheral veins and arteries.[21,22] It is interesting to speculate that propranolol may act in RSD in part by diminishing the effects of increased sympathetic nerve activity on peripheral veins and arteries that occurs in RSD.

Herpes zoster infection can precipitate RSD in the lower extremities. This important history should be obtained in the differential diagnosis of a painful swollen extremity, especially in older adults. This case also supports the suggestion that propranolol is successful in the treatment of reflex sympathetic dystrophy and probably should be instituted early in the course of illness along with aggressive physical therapy.

Summary

Reflex sympathetic dystrophy is a syndrome characterized by painful swelling of an extremity. It is thought to result from increased sympathetic activity in the autonomic nervous system in response to an injury, but the exact cause remains unknown. A case of reflex sympathetic dystrophy of the left ankle and foot secondary to herpes zoster infection in a 72-year-old man is reported. Of particular interest was the dramatic response to propranolol therapy after conventional RSD treatment failed.

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Refer to: Cummings P, Lysgaard M: Cardiac arrhythmia at high altitude. West J Med 135:66-68, Jul 1981

Cardiac Arrhythmia at High Altitude

PETER CUMMINGS, MD
MELODY LYSGAARD, C-CPT
Visalia, California

IN PATIENTS with the sleep apnea syndrome, 24-hour electrocardiographic monitoring has shown a typical pattern of cyclic sinus arrhythmia in which the heart rate slows dramatically during apnea and increases when airway obstruction is relieved.[1,2] In this study a single subject was monitored at high altitude and this same pattern was found, suggesting that hypoxia, probably aggravated by periodic breathing, may be sufficient to produce pronounced sinus arrhythmia and sinus bradycardia in an otherwise healthy person.

Report of a Case

One of the authors (P.C.) was the subject of this study. At age 34, he had had 12 years of mountain climbing experience including successful ascents of two peaks higher than 6,000 meters and one summit higher than 7,000 meters. He had experienced the syndrome of acute mountain sickness[3-5] either when ascending in a single day from sea level to about 3,600 meters or on expeditions when first arriving at altitudes of about 5,000 meters.

The present study was undertaken as part of an expedition to Annapurna (8,078 meters) in Nepal. A 24-hour electrocardiographic (ECG) study was done in California on July 20, 1979, at an altitude of 100 meters. Two leads, CC5 and

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Submitted, revised, March 12, 1981.

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CM5, were recorded on an Oxford Medilog 4-24 Holter recorder (Abingdon, England) and scanned on an Oxford Medilog ECG analyzer. Findings included no premature ventricular beats and 2,584 (108 per hour) premature atrial beats. The subject has been known to have frequent premature atrial beats since at least 1966. Heart rate varied from 118 (climbing stairs) to 43 during sleep); longest R-R interval was 1.4 seconds. In sleep, mild sinus bradycardia and sinus arrhythmia were noted. Except for the relatively high frequency of atrial premature beats, these findings are similar to those in a normal population.[6]

On August 12 the subject began the hike to Annapurna base camp. The hike began at 800 meters and on August 24, he reached base camp at 4,350 meters. On August 29 the subject began sleeping at camp I at 5,030 meters. On August 31 a repeat 2 channel Holter study was done for 18.5 hours while sleeping at camp I (5,030 meters) and carrying a load of 17 kg to camp II at 5,560 meters. One premature ventricular beat and 921 (50 per hour) atrial premature beats were noted. At 5,560 meters, sinus rhythm with rates up to 150 was noted while the subject was climbing or shoveling snow.

During sleep, pronounced cyclic sinus arrhythmia was noted. Heart rate was frequently in the 30's with R-R intervals of up to 3.3 seconds (see Figure 1). Rapid changes in heart rate were noted in a cyclic manner.

The subject was receiving no medication at the time of either study.

Later during the expedition, the subject lived for two weeks above 6,090 meters and reached a height of 6,970 meters. The only symptoms of altitude illness were experienced at camp I on September 1, where a severe headache occurred which lasted several hours. This condition resolved following rest and drinking fluids. Further Holter studies were not undertaken because an avalanche occurred, which killed three expedition members and swept away the recording equipment.

Although periodic breathing was not noted in the subject during sleep on Annapurna, it had occurred during sleep at altitudes as low as 3,200 meters on other mountains.

Discussion

Sinus bradycardia in sleep, with sinus arrhythmia and, occasionally, with second degree heart

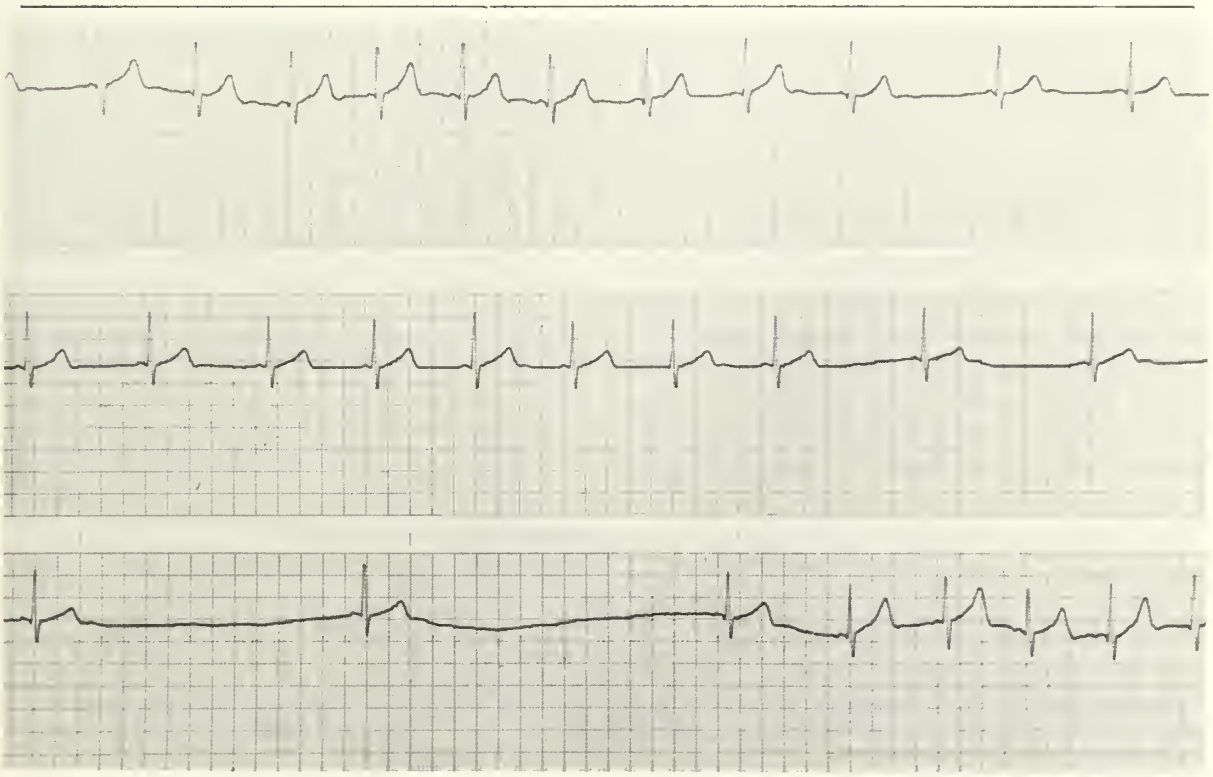

Figure 1.—Continuous electrocardiographic record of lead CM5 recorded in the subject during sleep at an altitude of 5,030 meters. Record shows pronounced sinus arrhythmia with R-R interval up to 3.3 seconds.

block, is a well-known occurrence in normal subjects.[6,7] The reported cases suggest that this is an event only occasionally noted during a sleep study in normal subjects. This has been the experience in our own Holter scanning laboratory. In the present study, however, the pattern is one of pronounced cyclic sinus arrhythmia occurring throughout the night, much like that reported in patients with sleep apnea syndrome. Tilkian and co-workers[1,2] have suggested that this pattern of sleep-associated arrhythmia is virtually diagnostic of the sleep apnea syndrome and that it is almost always associated with upper airway obstruction. They did note, however, that in one of their patients with poliomyelitis the arrhythmic pattern occurred with apnea that was centrally induced and not related to airway obstruction.

In healthy subjects monitored in sleep at 5,360 meters, pronounced periodic breathing has been noted, occurring about 80 percent of the time during sleep. During the apneic periods profound hypoxemia with saturations down to 61 percent were noted. Heart rhythm in these subjects was not reported.[8] In another study at 4,300 meters, periodic breathing was noted during 35 percent of sleep time.[9]

It seems most likely that at 5,030 meters our subject had hypoxia which resulted during sleep in periodic breathing caused by a central nervous system mechanism. During apneic cycles vagal stimulation produced sever sinus bradycardia, while later ventilation and relief of hypoxia resulted in speeding of the sinus rate. This theory is consistent with data recorded by Reite and colleagues[10] at 4,301 meters. They studied sleep at high altitude and noted bradycardia associated with apnea during periodic breathing. The changes they noted were not as dramatic as those in the present study, possibly because the altitude was less. Thus, it appears that hypoxia induced by high altitude can reproduce the arrhythmias seen in the sleep apnea syndrome. Tilkian and co-workers[2] have reported the case of one patient with poliomyelitis who had arrhythmias related to sleep apnea rather than airway obstruction. Even in those patients with upper airway obstruction a central nervous system mechanism plays a role in allowing the obstruction to occur.

Further study of arrhythmia at high altitude is indicated. It is worth noting that in this study it was easy to climb and carry loads with the monitoring equipment. Study of other patient groups with neurologic or cardiopulmonary disorders (or both) and periodic breathing is likely to show similar rhythm disturbances during sleep.

Summary

In a 34-year-old man, pronounced cyclic sinus arrhythmia occurred throughout sleep at 5,030 meters. This arrhythmia is identical to that seen in the sleep apnea syndrome.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Factors in Preventive Medicine

To the Editor: It is encouraging in the article on preventive medicine by David Maron[1] to see that a medical student is showing so much interest in that field and has reviewed the literature so extensively.

Perhaps he is unaware of the fact that for at least 25 years many of us have used periodic screening methods rather than "the traditional annual examinations." Primary physicians' offices have also long been places for helping patients change their life habits.

In regard to his suggestion that primary and secondary prevention are more important than tertiary, is there any evidence this is true? All three are important. Many people will not seek medical attention until there is a problem. Ongoing management of hypertension for example, has already been shown to be useful in reducing noncoronary events (from 55 percent to 18 percent in five years in a 1970 Veterans Administration study[2]).

Mr. Maron's point that we need to evaluate successes and failures is good. However, outside of a group setting or institution, who is going to pay primary physicians to keep and analyze statistics?

Perhaps one of the most important factors in prevention is not mentioned in this article—the environmental and social impact of factors that we cannot control, but can only strive to change. For example, how can we talk about good nutrition while there are still thousands of hungry people in our society? Would assuring an adequate income for all people do more in prevention?

MARJORIE M. WILSON, MS (PreventMed), MD
Yakima, Washington

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Ballistics Information in Gunshot Wounds

To the Editor: It was very interesting to read the report by Drs. Dart, Braitman and Larlarb on gunshot wounds of the descending thoracic aorta[1] in the May issue.

I felt one should call attention to the fact that information concerning the ballistics of the particular injuries was not included in the case presentation. Such information as caliber, length of barrel, bullet configuration and distance of the weapon from the victim are critical factors that determine the outcome and survival in such cases. The hypervelocity calibers that are now being used are causing terrible damage, often irreparable. The hypervelocity shock wave generated by these calibers do far more damage than the remaining entry or exit wound leads the eye to believe.

Dr. Dart and his co-workers should be commended on these "heroic saves"; however, more ballistics information should be included in the medical literature discussing gunshot wounds in order to understand the mechanism of injury.

JAMES S. SIMON, MD
Tiburon, California

REFERENCE

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Editor's Note: Two articles and three letters bearing on Dr. Simon's comments have appeared in the journal in the past several years. The three letters, under the title "Facts on Ballistics," appeared in the November 1978 issue, page 437. The two articles are as follows:

1. Wilson J: Wound ballistics (Trauma Rounds). West J Med 127:49-54, Jul 1977
2. Wilson JM: Shotgun ballistics and shotgun injuries (Trauma Rounds). West J Med 129:149-155, Aug 1978

The Human Computers

To the Editor: "Buy your next car from us—we have computers on board!" This is today's appeal from the auto industry. Yes, we can have tomorrow's automobile today, armed with computers that are capable of telling us how far we are from our destination, what time we will arrive and whether we have enough fuel to take us there.

Each day the mail brings us flyers describing

office computers that can be programmed to bring greater efficiency into our office practices. We are even led to believe that all future kitchens will have their own computers. The Japanese are sending us tiny computerized TV sets no larger than a cigarette package. Recently television has brought into our living rooms bank upon bank of computers that guided Columbia into outer space.

What wonders our scientists and our engineers have wrought—almost beyond belief. But have we ever stopped to contemplate the even greater wonders of the computerization we carry around in our bodies? In comparison to the electronic wizardry in our central nervous system Detroit's solid-state black box computers are primitive calculators.

It has long been known that the central nervous system is a complex electrochemical communications apparatus, capable of transmitting instantaneous messages throughout our bodies. Now, the electron microscope has enabled us to look inside the individual nerve cell, the neuron, with all its capabilities.

Electron microscopists peering through the neuron cell membrane, discovered a beehive of activity. Each of the 7 billion neurons, acting as separate biologic entities, are constantly sending out and receiving millions of computerized messages. Each neuron has some 5,000 neurotransmitters and neuroreceptors—our "on-board" computer— to guide and regulate every body function.

The substances we feed into our body's computer, whether food, water, oxygen or drugs, are promptly acted upon as programmed. Ten years ago research workers at Stanford discovered that the impulses received by the neuron were acted upon by "receptors." A chemical, whether food or drug, acting upon these receptors, could elicit either an "excitatory" or "inhibitory" response. An excitatory impulse could result in pleasure and enhanced body function. An inhibitory impulse could be blocked by the neuron, producing what we recognize as pain, anger, anxiety. The neuron might even produce endorphin—inner morphine —to relieve mental anguish. This keeps us humble. We are reminded of the responsibility we shoulder as we go about caring for our patients' minds and bodies.

We all witnessed a frustrating two-day delay in the launching of the space shuttle when the master computer and the backup computers were sending each other scrambled messages. Are we aware, always, that the drugs we prescribe and the chemicals we administer to our trusting patients may send garbled or blocking messages to their neurons? Will we harm or injure these ultrasophisticated human computers?

We envy those automotive engineers in Detroit. They can take out, look at and repair a solid-state black box. Ours is the awesome responsibility of manipulating, protecting, preserving 7 billion delicate, intangible nerve cells. That's a responsibility not to be taken lightly.

E. R. W. FOX, MD
Special Editor for Idaho
Coeur d'Alene, Idaho

A Case in Point

To the Editor: I have just finished reading your editorial "Financial Aid for Medical Students."[1] I am just completing my first year at the University of Southern California School of Medicine and am one of the medical students to whom you are referring in your editorial. I already have $10,500 in loans. More important, however, I have a real concern about how I will get enough loan money to complete my education. Tuition next year is more than $9,400 and, with books, supplies and living expenses, my budget approaches $18,500. The school can only be of minimal assistance, and with expected changes in government programs, I cannot count on getting enough money to meet my needs, either next year or in the years following.

First, I want to thank you for bringing this problem to the attention of physicians in practice. Second, should any of these physicians show an interest in "assisting needy medical students," I would appreciate it if you would give them my name and address.

DEBORAH OLES, MSW
Los Angeles

REFERENCE

1. Financial aid for medical students (Editorial). West J Med 134:440, May 1981

Violence by Handguns—Commentary

To the Editor: The editorial concerning violence by handguns[1] aptly pointed up the precondition behind the epidemic of death by firearms in remarking on this nation's "infatuation with violence . . . [through] entertainment. . . ." Violence via television and motion pictures *reflects* but does not *cause* our national preoccupation with guns. The problem is primarily in the national psyche and secondarily in handgun control, which I also believe is a necessity.

However, my interest is in the public's uncon-

scious and conscious participation in violent crime as measured by the persistence, even flowering, of crime movies featuring violent death. In a recent address, before the Academy of Forensic Psychiatry (New Orleans, May 10, 1981),[2] I proposed the rewriting of crime stories on television in such a way as to expose the public's fascination with violence through entertainment vehicles. Since our society loves its crimes but hates its criminals, television dramas should illuminate this psychologic background of our feelings and hence permit them to be viewed objectively. Entertainment is a more powerful medium than preachment or exhortation, and television admittedly is our most powerful persuader.

A rewriting of violence dramas may take a generation to reorient the American public to its own aggressive nature. This sugarcoated therapeutic experiment (via entertainment) would be sobering to the coming generation from whom assaultive criminals will emerge. As it is, the writers' presentations cater to our aggressive impulses almost automatically. Skillful writers and directors could turn the stories around so that the true psychological state of affairs would be presented with no loss in entertainment value and a great gain in insight. Such an attempt could not help but be a factor in time in the prevention of violence.

WALTER BROMBERG, MD
Sacramento, California

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1. Violence by handguns (Editorial). West J Med 134:438, May 1981
2. Bromberg W: Law and psychiatry—A stormy marriage. Bull Am Acad Psychiatry Law, In press, 1981

* * *

To the Editor: Attempts to thwart the "agents of transmission" of illegal drugs into our country are made daily (even if not always successfully) by all agencies of government. Similar efforts to minimize, if not curtail, the unlawful use of handguns should also be made. The medical profession belongs in the vanguard of such a crusade, despite some of the obstacles facing it, just as it has often been in its fight against disease.

The "acceptance and approval from the public at large" of the use of handguns which you bemoan in your editorial[1] in the May issue are the *defenses* employed by a concerned and frightened public. If the *gun lobby* was as concerned with saving lives as are doctors who must bear witness to the results of such carnage, the agents of transmission which masquerade under different colors would find their specious arguments short-circuited.

I invite you to help us grope toward a solution rather than for you to invite us to accept what you consider to be inevitable.

MURRAY KLUTCH
Berkeley, California

REFERENCE

1. Violence by handguns (Editorial). West J Med 134:438, May 1981

Management of Thyroid Nodules

To the Editor: The study by Miller, Abele and Greenspan on fine-needle aspiration (FNA) biopsy for thyroid nodules in the March 1981 issue[1] fails to show that FNA actually leads to avoidance of surgical intervention. In their proposed management plan it is apparent that if a nodule is "suspicious" on FNA biopsy an operation will be carried out. If it is not suspicious or benign then suppression is undertaken. If the mass does not regress it is removed.

This same plan of approach can be and has been undertaken without fine-needle aspiration. Whatever the FNA biopsy shows, if a solitary nodule persists it will be removed surgically.

FRANK P. BONGIORNO, MD
Martinez, California

REFERENCE

1. Miller TR, Abele JS, Greenspan FS: Fine-needle aspiration biopsy in the management of thyroid nodules. West J Med 134: 198-205, Mar 1981

* * *

The Authors Reply

To the Editor: Dr. Bongiorno's statement that use of fine-needle aspiration (FNA) does not avoid surgical procedures on benign thyroid nodules is an incorrect conclusion drawn from our decision matrix, Figure 9. The last box of that figure states that failure of a nodule to regress leads to *rebiopsy* or *excision* of the nodule. The rebiopsy option means nonsurgical clinical observation with repeat FNA as the clinician desires.

The advantage of FNA is that it is a rapid test which is done at no significant risk to the patient. If a nodule is clearly malignant or suspicious in a high-risk patient, there is no delay in surgical removal. On the other hand, if the nodule is clearly benign or suspicious in a low-risk patient, an operation may be avoided. In fact, surgical procedures were avoided in 101 of the 129 patients in this study who clinically had solitary cold nodules. FNA in conjunction with clinical evaluation provides improved selection of patients for medical surgical management of thyroid nodules.

THEODORE R. MILLER, MD
JOHN S. ABELE, MD
FRANCIS S. GREENSPAN, MD
San Francisco

Refer to: Davis JH, Brown DW: Adoption: Pediatric, legislative and social issues (Issues in Medicine). West J Med 135: 72-77, Jul 1981

Adoption: Pediatric, Legislative and Social Issues

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Physicians may find themselves involved in many phases of the adoption process, ranging from advising infertile couples who wish to adopt a child to caring for adopted children, adolescents or adults. Recent legislation has been aimed at making it possible for children to be adopted who have been receiving foster care and at providing financial assistance to implement the adoption of children with handicaps and with medical problems. The adoption process is becoming more open. Adoptees are searching for and finding their biological parents and all parties in the "adoption triangle" are developing relationships with one another.

IN THIS PAPER we examine the status of adoption in the United States, indicating some of the changes that have occurred in the past few years and suggesting some possible future trends.

Medical Issues

Physicians who practice pediatrics may become involved in the adoption process at various levels.[1-4]

Teenage Pregnancy

In caring for a pregnant teenager, the physician should discuss adoption as one of the alternatives to abortion or keeping the baby. Ideally, the discussion should include the girl's parents and her sexual partner. The doctor should also be knowledgeable about the social agency or agencies in the community to which the girl can be referred.

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Presented at the XVI International Congress of Pediatrics, September 12, 1980, Barcelona, Spain.

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Advising Potential Adoptive Parents

Infertile couples frequently contact a physician for information and, they hope, to find a source of adoption. Physicians need to be knowledgeable about infants and children who are available for adoption, and they should explain the features of independent and agency adoptions, identifying the local agencies that handle adoptions. Moreover, they should explore each couple's willingness and suitability for an older or handicapped child, not just a healthy newborn. It is usually a particular type of person or couple, however, who can successfully adopt some of these special children. Physicians should also advise couples to obtain infertility counseling before they seek to adopt, to resolve feelings arising from not being able to conceive a child of their own.

Pediatric Care of Babies to Be Adopted

Hospital-based physicians may be called on to examine and assess the health of an infant or child who is to be adopted. It is important not only to make a careful appraisal of the physical

and developmental status but also to collect as much medical history and as many background data as possible both from the records available and from the biological parents themselves whenever possible. It should be pointed out that information collected at this time may be invaluable to subsequent physicians or to the adopted child in later years. The question of sealed records and the role of adoption agencies will be discussed later. Many agencies are still very careful not to disclose identifying data, and it sometimes requires a bit of ingenuity to obtain the information desired. Needless to say, when the adoptee is transferred to the care of another physician the complete records should be forwarded as well.

Care of Adopted Children and the Adoptive Parents

Adopting a child is different than having one by birth. The sudden confrontation with parenthood instead of a nine-month pregnancy, continued feelings of inadequacy stemming from the state of infertility, the fear of losing the child to the biological mother and the fear of what might happen later as a result of the adoptee's search for identity all have to be dealt with in the ongoing care of each adopted child. Adoptive parents in general tend to be overprotective of the child as compared with natural parents. By anticipating, watching for and educating adoptive parents about these factors it is possible to prevent significant problems.

One point which should be specifically mentioned regards telling the child that he or she is adopted. There is still no unanimity among the experts as to how and when this should be done, but it is something that physicians should discuss with adoptive parents early. In all cases what is told to the child must be truthful and the information should be given early in life, simply at first and gradually in greater detail as the child asks more questions. It is probably wise for the physician, after first discussing it with the parents, to explore with the adopted child his feelings about being adopted and to further clarify any questions the child may have.

Teenage and Adult Adoptees

The teen years are often a period of turmoil. Many nonadopted teenagers express doubts about their ancestry: "You can't be my real mother, otherwise you would not be so mean to me!" Therefore, it is not unnatural for an adoptee at the same age to become restless and have questions about his identity. (This topic will be discussed in more detail in the last section of this paper.) It is proper to explore with the teenage adoptee his feelings, pointing out that some adoptees need to know about their ancestry while others do not care. It is important to provide him with some nonidentifying information if he is still underage and to offer to help him further, if he wishes, after he reaches maturity. When the adoptee reaches adulthood he should be given whatever information is available. If an adoptee is truly interested in searching for his biological parents, we can assist by securing his own hospital records and by referring him to an adoption group or organization that provides such help and support.

Helping With Legislation and Community Affairs

As will be discussed in the next section, important legislation regarding adoption issues is being developed by the federal government and by many states. The legislators need and welcome the help and support of knowledgeable physicians in the drafting and promotion of such legislation. The courts welcome testimony from these physicians as an aid in interpreting and administering the laws and, finally, the social service agencies are grateful for physicians willing to advise in specific cases or to serve on their boards or committees that deal with adoption problems.

Legislative Issues

The last few years have seen a major increase in the number of bills on adoption and related issues that have been introduced. At the federal level two major pieces of legislation were passed last year and a third measure became law this year. Together they reflect an involvement by the federal government in adoption and foster care far beyond anything previously on the statutes.

PL 95-266—The Child Abuse Prevention and Treatment and Adoption Act of 1979

This law has two main provisions that apply to adoption. It calls for the development of a National Adoption Information Exchange System. The object of this system is to collect data and disseminate information on adoption with particular reference to the so-called hard-to-adopt children. In addition, it establishes seven regional centers throughout the country, all coordinated through a central office in Washington,

DC. These centers are now in operation and are charged with the dissemination of information and the coordination of adoption efforts within and among the respective regions.

It also calls for the writing of a Model State Adoption Act. To this end it has mandated the appointment of a panel of 17 members from diverse fields who have had a series of meetings and who have written a draft, which has been published in the *Federal Register*.[5] There have also been regional hearings on the items included in the proposed act, where mixed reactions to some of the recommendations have been voiced. The Act affirms that adoption is the best means for providing family life for children when their biological parents cannot do so, that if adoption is impossible, legal guardianship is second best, and that adoptees' rights prevail in a conflict.[6] The express purposes of the Act call for adequacy of adoption services for all children in need, prompt legal procedures for terminating parental rights, removal of obstacles to adoption including subsidy for children with special needs, identification of children in need and case review. It calls for the preservation and accessibility of records including the availability of all sealed birth records to adoptees 18 years of age and older.

The final recommendations may be altered as a result of the regional hearings. And, if enacted into law, it will serve as a guide to the various states because adoption services are really regulated at the state level.

SB 2561 (Levin)—The Adoption Identification Act of 1980

This bill introduced into the US Senate, although not enacted, would have amended PL 95-266, discussed above, by adding Title III, Adoption Identification. SB 2561 sought to enable biological parents or other relatives of an adoptee and the adoptee, with mutual consent, to locate each other through a centralized computer system. Similar registers are now in operation by various search organizations. Had this bill been enacted, it would have been the first such registry approved by law.

PL 95-608—The Indian Child Welfare Act of 1978

This is a controversial piece of legislation which in principle is designed to protect the best interests of Native American children. In actuality, it turns over much control to tribal courts and restricts adoption of Native American children for the most part to Native American families, with the result that the rights of the parents and of the adoptive custodians have priority. Further, there are conflicts between the tribal court system and the state court systems in the Act. The Act also, for the first time in federal legislation, called for the right of the adult adoptee (aged 18 or older) to have access to his birth records.

PL 96-272—The Adoption Assistance and Child Welfare Act of 1980

This law is a companion and supplement to PL 95-266. It mandates state adoption subsidy programs and provides federal matching funds for child welfare services. It calls for the development and implementation of preventive and reunification services as well as protective measures designed to keep families intact. At the time of preparing this paper, an appropriation bill to provide funds for this act had not yet been passed.

Social Issues

In the 1940's there was an ample supply of newborn babies available for adoption. Unwed mothers were generally happy to be able to give up their babies to couples who promised to give them a good home; likewise, couples who found themselves infertile were glad to adopt them. This was an "adoptive parents market." Everything was done to make the adoption as much like a birth as possible: anonymity of biological parents, promise of nondisclosure of identity, sealed records with the issuance of a new birth certificate naming the adoptive parents as parents, and, in many instances, never telling the adoptee of his or her true status. The rights and feelings of the adoptees were disregarded by the courts, the social agencies, and by society in general, under the guise that they, the adoptees, were so lucky to have a fine stable home and family that a bit of deception was justified.[7-9]

The 1960's and 1970's saw a change in the social order. Birth control and abortion both became more available. Single, unwed mothers began keeping their babies rather than putting them out for adoption. All of these factors played havoc with the adoption market, and the demand became far greater than the supply. Black market adoption operations sprang up with fees of $10,000 to $100,000 reportedly being paid by couples eager to adopt.[10] Foreign adoptions increased, with babies being supplied from Central and South

America as well as from Korea and Vietnam. Special agencies emerged, such as Holt International Childrens Services, to handle these adoptions. At the same time, the adoption of older and handicapped children became more prevalent, although couples desirous of adopting newborn infants were usually not satisfied with these alternatives. More recently, states and the federal government have legislated subsidies to implement the adoption of such children.

Legal adoptions have been handled both through licensed social agencies and independently. In an agency adoption a baby is turned over to the agency, which often places it in temporary foster care until the "proper" adoptive parents can be found. In an independent adoption, carried out through a private attorney, the babies are usually turned over at birth to the adoptive parents who may or may not have met or learned the identity of the biological mother, and vice versa. The agencies, particularly, have felt duty bound to preserve the anonymity of the biological parents as well as the placement of the child. Both methods of adoption still exist.

Today most adoptions are independent. Many workers in the field argue against independent adoptions on the grounds that the welfare of the biological mother is often ignored, that there is inadequate screening of the adoptive parents and that there may be third-party profiteering in the operation. Attempts are being made through legislation to correct some of these problems. Adoption agencies are both governmental and private (voluntary). In California, for example, the state and county agencies are placing less emphasis on adoption of normal newborns, turning these over to the voluntary agencies, such as the Children's Home Society of California. Instead, they are concentrating on the placement of children released by the courts and of older and handicapped children. They are being assisted in this effort by special agencies such as Family Builders by Adoption, a subsidiary of the North American Center on Adoption, by the recently mandated National Adoption Exchange and its regional centers. In all of this, the emphasis is being placed on finding a home for a child in need rather than satisfying the needs and expectations of the childless couple. Also, and again with the impetus of appropriate subsidies, efforts are being made to free for adoption children who are now in foster and temporary care when it is apparent that return to their own homes will not be possible.

At the same time that the above changes were occurring in the adoption field,[11,12] adult adoptees and then others in the adoption triangle—the biological mothers and adoptive parents—began to make themselves heard. Adoptees voiced the claim that they had a moral and a legal right to learn of their birth heritage, and that the past secrecy and anonymity were invalid on the grounds that these decisions were made at a time when they could not give their consent.

Pioneers in the adoption field included Jean Paton, a social worker, herself an adoptee who described her successful search for her birth mother in a book, *Orphan Voyage.*[13] Within an organization of the same name, Jean Paton operates a registry for adoptees and birth parents trying to locate each other and also publishes a newsletter. In a Book of the Month Club selection *(The Search for Anna Fisher*[14]*),* Florence Fisher, a New York housewife, describes finding her biological parents. She founded ALMA (Adoptees Liberation Movement Association) in New York City; the organization now has chapters throughout the country. ALMA, through a professor at New York Law School, Cyril Means, is bringing suit in the US Federal District Court to have the laws regarding sealed records declared unconstitutional. Margaret Lawrence, another pioneer in this field, founded Yesterday's Children and has written and lectured extensively on adoptees' rights and feelings.

Biological parents have been a bit more reluctant to speak up because, historically, agencies have led them to believe that they must remain silent. Many, however, although unwilling to make an active search on their own behalf, have hoped that their children would some day seek them out. Gradually, biological parents have become more comfortable in espousing their cause and have formed groups such as CUB (Concerned United Birth Parents) to speak on their behalf. These biological mothers tell us that in giving up their children for adoption they nevertheless continue to feel a deep concern for their welfare, and most welcome a reunion when these children have grown up.

Parents have, for the most part, been fearful of losing their adopted children as a result of the children's search activities and have felt threatened by the thought of the biological mothers being reunited with their children. Adoptive parent groups have developed both as a defensive effort to combat these implied threats, and to speak up

against legislation aimed at opening records and against facilitating reunions. Also, they have organized for mutual support and assistance in meeting the special demands of parenting.

We would like to describe a new type of organization with which we are experiencing very good results. One of these, the Post Adoption Center for Education and Research (PACER), was founded by one of the authors (D.W.B.), himself an adoptee. PACER serves all the members of the "adoption triangle," and the community, both lay and professional. PACER is engaged in a program of research in collaboration with Stanford University's Dr. Robert Hess, designed to study the beliefs that parents of adopted children have concerning factors that influence the developmental, social and academic growth of these children.

PACER is different from other types of organizations in that it represents the perspective of and includes all three sides of the "adoption triangle." It builds on the connections among all parties to the adoption process. It provides support groups for adoptees, adoptive parents and the biological parents. Awareness and understanding of the complexities of the adoption experience and its lifelong impact on those involved is a central PACER goal.

We have found that contrary to popular belief, the biological parents do not forget the child they relinquished and want very much to know how he or she has grown up. The relinquishment of the child is usually a rejection of the circumstances, not a rejection of the child. All three sides of the "adoption triangle" experience separation and loss and those involved are uniquely tied together by issues of identity and a sense of shared loss—loss for the adoptive parent due to infertility, and not being able to give birth to this child, loss for the biological parent due to relinquishment and not being able to raise this child, and loss for the adoptee in the separation of the biological and parenting tie. We believe that the searching is a quest for information to heal this loss, not an attempt to find new parents. Popular opinion supports the idea that the adoptee's search represents a repudiation of the adoptive parents. The truth seems to be very different, for searching appears to have the opposite effect. It evidently strengthens the bond between the adoptee and the adoptive parents.

PACER is also finding that the adoption experience need not be shrouded in secrecy and denial. With support and guidance, members of the "adoption triangle" are gaining insight and understanding, and with the help of community leaders and professionals, the image of "adoption" in the public eye can be changed and improved.

The Future

The authors believe that adoption practice and experience in the years ahead will continue to change in the direction of openness and flexibility. Agencies, we feel, will continue to expand their programs of postadoption services as the biological parents, adoptees and adoptive parents seek assistance in parenting and coping skills. It is to be hoped that relinquishment will involve contact between the biological parents and the adoptive parents and a commitment to support the adoptee in his or her search once the age of majority is reached. The exchange of medical information at the point of adoption and the updating of those records could become standard practice, with the biological parents providing much more data about themselves and their families than has been the practice in the past. The authors are convinced that the need to pretend that the adoptive relationship is a biological one will change and that there will be a recognition that the adoptive relationship is a strong and viable one in its own right.

State legislative reform seems to be gaining momentum as a result of the Model State Adoption Act as provided by PL 95-266. As states begin to allow access by the adult adoptee to his or her sealed adoption records, all concerned should find that this has a positive effect on the entire adoption community. Access to those records, with consent of the biological parents, will probably be a transitional step in the process of legislative reform in the years immediately ahead.

The federal government is continuing to offer enhancement in the adoption of both hard-to-place children and those waiting in foster care by providing adoption subsidies and support for community and volunteer efforts.

Discussion

Adoption is considered the most desirable situation for any child who has no other home of which he or she is a part. The easy availability of newborn infants to be adopted no longer exists. Many more childless couples wish to adopt than can be accommodated. A change in emphasis and perspective has occurred in recent years so that now the primary concern is for the child being

placed for adoption rather than for the adopting parents. To this end there has been more emphasis on the adoption of older children and of children with physical, developmental and emotional handicaps as well as for the adoption of children who have been placed in foster care. To case the financial burden of adopting these "special" children, some states have enacted legislation which subsidizes the adoptive parents for medical and other expenses connected with their care.

Intercountry adoptions are being carried out but with more control and restraints than formerly. Legislation is being directed to curb black market adoptions, to supervise independent adoptions more closely and to safeguard the rights of both biological parents in their relinquishment of a child for adoption.

Physicians are in a unique position to serve various roles in the adoption process, such as advising prospective adopters, counseling pregnant women about giving up babies for adoption, examining babies to be adopted, and advising adoptive parents who want to do a better job of parenting. Outside of their own practice, pediatricians can be invaluable to social agencies, the courts and the legislatures as consultants and as adoption advocates. They can advise and support their adolescent and young adult adoptees who are searching for their roots and can be a community resource in this field as well.

In the past ten years or so, special interest groups have formed to promote the interests of adoptees, biological parents and adoptive parents in the search for identity. Both the adoptee groups and the biological parent groups have pressed for legislation to "open" records (which have been sealed) in order that reunions between adoptees and these parents might occur.

The Post Adoption Center for Education and Research in Palo Alto, California is a unique organization designed to represent all involved in adoption—the biological parents, adoptees, adoptive parents, pediatricians and other professionals. It views the entire adoption experience in a broad perspective, disseminating that information to the community and to the professions.

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Refer to: Kahn AM, McCrady-Kahn VL: Molten metal burns (Information). West J Med 135:78-80, Jul 1981

Molten Metal Burns

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Molten metal burns are a frequent industrial injury among workers in foundries. The injury is typically small but very deep. Usually the depth and seriousness of these injuries is not recognized immediately by emergency department or industrial clinic physicians.

In caring for 16 patients with molten metal burns we found that the burns were full thickness and averaged 2.7 percent of the total body surface (0.5 percent to 23 percent). The average hospital stay was 17 days, and ranged from 7 to 68 days.

These small but serious burn injuries can result in tremendous loss of work days for both patients and employers, as well as tremendous expense to industrial insurance carriers. Almost all of the expenses for medical care before admission to hospital as well as a third of employee compensation benefits could be eliminated if definitive treatment was immediately available to these patients.

THE INCIDENCE of industrial burn injuries is on the decline as the result of increasing awareness of hazards and the enforcement of safety regulations. However, foundry workers continue to have a high risk of molten metal burns. Of interest is the relative absence of papers on molten metal burns in the medical literature; only one paper in English was found that discussed the topic.[1]

Sixteen patients, despite the use of protective clothing and shoes, were burned by molten metal in local foundries and were treated in our facility over seven years. All but one of these patients were initially cared for by local industrial medical clinics. The time between initial care and referral of these 15 patients ranged from 6 to 41 days. In our experience, the severity of molten metal burns is generally not appreciated. Consequently, definitive treatment is often delayed. This delay results in prolonged morbidity and unnecessary expense.

From the Brotman Medical Center Burn Center, Culver City, California.

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Patients

Between 1972 and 1979, a total of 16 men with molten metal burns were cared for. The patients ranged in age from 19 to 57 years. The extent of the total body surface burned ranged from 0.5 percent to 23 percent (mean 2.7 percent). None of the patients had superficial burns. All of the burns were either very deep partial thickness or full thickness, confirmed by histopathologic examination of tissues removed at the time of operation.

Only 1 of the 16 patients was admitted to hospital immediately (the patient with 23 percent total body surface area burn). The interval be-

tween the time of injury and referral to our hospital for the remaining 15 ranged from 6 to 41 days—an average of 22 days. Time in hospital ranged from 7 to 68 days—an average of 17 days. Following discharge, additional convalescence required an average of 32 days and ranged from 5 to 105 days. The work time lost ranged from 24 to 175 days and averaged 69 days (Table 1).

All patients were injured during the course of their employment, and expenses for each patient were covered by Worker's Compensation insurance. Complete financial information was available on 10 of the 16 patients. For these 10 patients the total medical expense averaged $7,595 ($2,247-$26,797). The disability benefits that were paid averaged $2,759 ($308-$11,026) (Figure 1).

Treatment

Aggressive treatment was initiated by either excising the burn wound to fascia or tangentially excising the burn wound and immediately applying meshed split-thickness skin grafts.

This type of burn wound is usually found on the lower extremities, where use of a pneumatic tourniquet may be beneficial. When the tourniquet is not used, perfect hemostasis must be obtained before applying the skin grafts. When the pneumatic tourniquet is used, the burn is excised and the skin graft applied with a compression dressing before the tourniquet is deflated and removed. The initial dressing change is done on the third or fourth postoperative day.

Skin grafts on all of the patients survived satisfactorily with 100 percent graft take. Patients with skin grafts on the lower extremities were kept in bed for six to ten days. At the time of discharge each patient was measured so that an elastic garment could be specially made to cover the skin grafted area. The patients were instructed to wear these garments continuously for six months to a year.

Discussion

Foundry workers are frequently burned by molten metals. In this series of patients, burn size

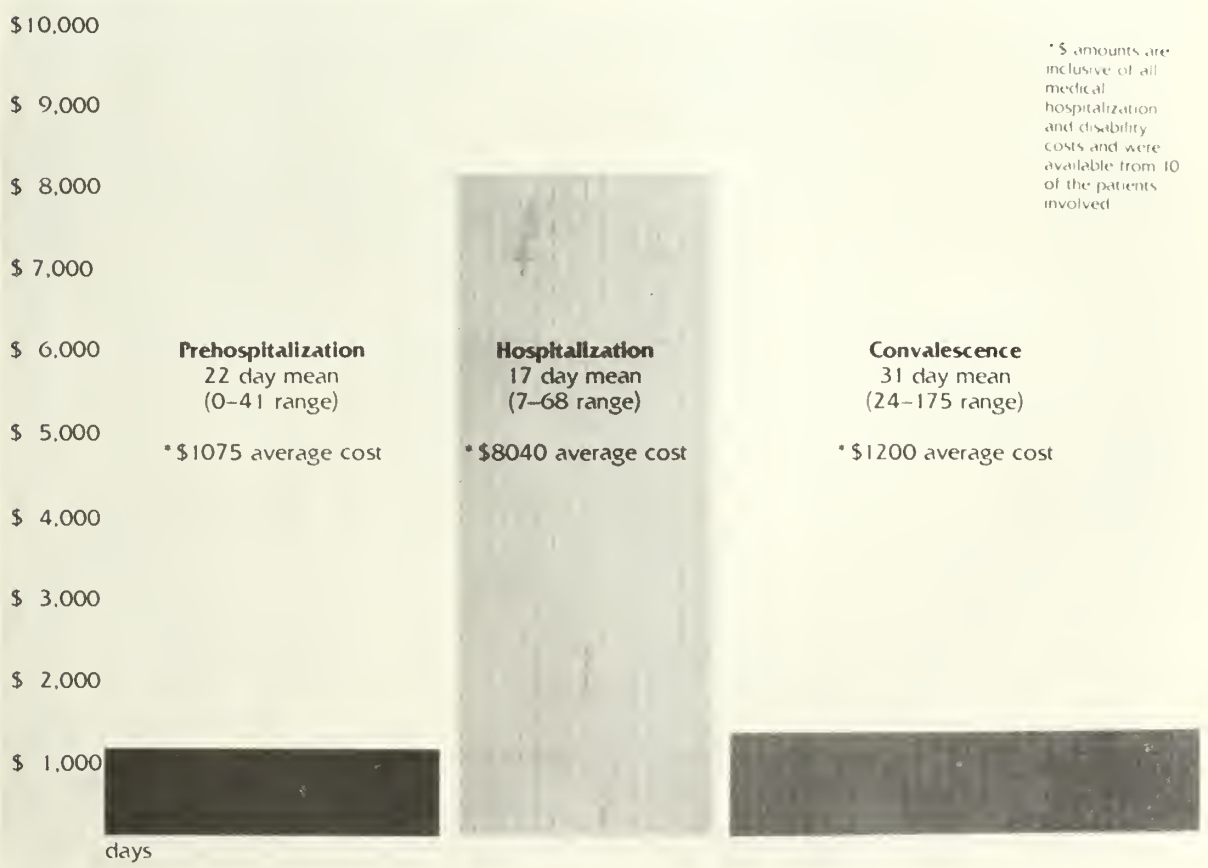

Figure 1.—Expenses and time required for care before admittance to hospital, care in hospital and convalescence following discharge for ten patients with molten metal burns.

TABLE 1.—*Summary of Time Required for Care of 16 Patients With Molten Metal Burns*

	Mean	*Range*
Age (years)	36	19-57
Extent of burn (percent)	2.7	0.5-23
Time before admittance to hospital (days)	22	6-41
Days in hospital	17	7-68
Convalescence after discharge (days)	32	5-105
Lost work time (days)	69	24-175

averaged 2.7 percent of the total body surface. If the patient with a 23 percent body surface area burn were to be excluded, then the average burn size would be only 1.4 percent of the total body surface area. These burn wounds are almost always full thickness and initially the pain is slight to moderate. Probably a combination of the small area involved and the lack of initial severe pain causes the industrial clinic and emergency room physicians to misjudge the depth of the burn wound. Consequently, these patients are either returned to their work or sent home. They are often treated on an outpatient basis by an industrial clinic or emergency room for varying periods of time. During this time increasing pain due to edema and inflammation usually develops. It is the patient's complaints and lack of healing over an average of three weeks that result in the recognition of the true severity of the injury and, thus, referral for definitive treatment.

In this series, the average total disability time of 69 days could have been reduced by approximately a third if the nature of these injuries had been recognized immediately and surgical management promptly initiated. Also, based on the financial data of the ten cases, it appears that a third of the disability benefit payments and the medical expenses before hospital admittance could have been eliminated, reducing the total financial cost by 10 percent.

Summary

More adequate education of industry, medical personnel and insurance carriers will result in decreasing the interval between injury and definitive treatment and, consequently, will reduce suffering of the victims, medical expenses and disability payment expenses.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Phenytoin Metabolism in Pregnancy

Kochenour NK, Emery MG, Sawchuk RJ

Obstetrics & Gynecology
56:577-583, Nov 1980

DISCIPLINES: Obstetrics, Gynecology, General Practice, Family Practice

READABILITY: Very good

The increased likelihood of epileptic seizures during pregnancy is judged to be a result of impaired metabolism of phenytoin (Dilantin). The authors recommend that the dosage be increased by small increments as the pregnancy progresses. Phenytoin as well as the disease itself, may be teratogenic but fetal hypoxia during seizures poses a comparatively greater danger to the infant.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Transcanal Labyrinthectomy for Intractable Vertigo

Hammerschlag PE, Schuknecht HF

Archives of Otolaryngology
107:152-156, Mar 1981

DISCIPLINES: General Medicine, General Surgery

READABILITY: Very good

An excellent presentation with well-organized, clearly written material.

Wegener's Granulomatosis and Polymorphic Reticulosis —Two Diseases or One?

McDonald TJ, DeRemee RA, Weiland LH

Archives of Otolaryngology
107:141-144, Mar 1981

DISCIPLINES: General Medicine, General Surgery

READABILITY: Very good

Timely, well presented and documented material.

—ROGER BOLES, MD
San Francisco

Biotin Deficiency: An Unusual Complication of Parenteral Alimentation

Mock DM, DeLorimer AA, Liebman WM, et al

New England Journal of Medicine
304:820-823, Apr 2, 1981

DISCIPLINES: Pediatrics, Nutrition

READABILITY: Excellent

The clinical manifestations of multiple carboxylase deficiency, erythematous rash, alopecia and hypotonia may be seen in patients with short gut syndrome treated with long-term parenteral alimentation unless the solutions employed are supplemented with biotin. Chronic antibiotic use may contribute to this problem.

—WILLIAM L. NYHAN, MD
San Diego

Biotin-Responsive Carboxylase Deficiency Associated with Subnormal Plasma and Urinary Biotin

Thoene J, Baker H, Yoshino M, et al

New England Journal of Medicine
304:817-820, Apr 2, 1981

DISCIPLINES: Pediatrics, Genetics, Nutrition

READABILITY: Excellent

An infant or child presenting with an erythematous rash, resembling acrodermatitis enteropathica or zinc deficiency, and with alopecia totalis, keratoconjunctivitis, developmental delay and ataxia may have multiple carboxylase deficiency in which the fundamental defect is in the handling of biotin which is required for biologic carboxylations. Treatment with 10 mg per day of biotin reverses all of the manifestations of the disease. There appear to be two forms of the disease, an early infantile form and a later form in which the abnormality may be associated with low concentrations of biotin.

—WILLIAM L. NYHAN, MD
San Diego

Reduction by Naproxen of Excessive Menstrual Bleeding in Women Using Intrauterine Devices

Davies AJ, Anderson ABM, Turnbull AC

Obstetrics & Gynecology
57:74-78, Jan 1981

DISCIPLINES: Obstetrics, Gynecology, Family Practice

READABILITY: Very good

Excessive uterine bleeding is a complication associated with the use of an intrauterine contraceptive device (IUD). *These authors showed in a double-blind placebo-controlled crossover study that the administration of 250 mg of naproxen (Naprosyn, Syntex) three times a day for five days during the menses resulted in a 50 percent reduction in blood loss.*

—E. R. W. FOX, MD
Coeur d'Alene, ID

Malignant Tumors of Salivary Glands—A University Experience

Boles R, Raines J, Lebovits M, et al

The Laryngoscope
90:729-736, May 1980

DISCIPLINES: General Medicine, General Surgery, Otolaryngology

READABILITY: Very good

Well-presented timely article clearly written and understandable. Particularly of interest to specialists and others in the disciplines.

—ROGER BOLES, MD
San Francisco

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

PROTOCOLS FOR PREHOSPITAL EMERGENCY MEDICAL CARE—Jean Abbott, MD, Emergency Physician, Boulder Community Hospital, Boulder, Colorado; Marilyn Gifford, MD, Emergency Physician, EMS Coordinator, St. Joseph's Hospital, Denver; Clark Chipman, MD, Chief, Emergency Services, Emmanuel Hospital, Portland, Oregon; Joseph Engelken, MAPA, Program Director, Emergency Medical Training, School of Allied Health, University of Kansas Medical Center, Kansas City; and Peter Rosen, MD, Director, Division of Emergency Medicine, Denver General Hospital, Clinical Professor of Emergency Medicine, University of Orgon. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202). 1980. 191 pages, $11.95 (softbound).

As the title of this book suggests, it presents information that readers should become well acquainted with before an emergency situation arises. Here is a paperback, concisely prepared in outline form, that shows how to develop protocols for prehospital emergency medical care. Designed for people who have had previous clinical experience, it stresses the use of common sense in the treatment of patients before they come to a hospital. It is not a book for amateurs or lay persons, but is directed primarily toward paramedics and emergency medical technicians. It would also be helpful in the teaching of medical students and residents, and its usefulness for attending physicians who need to develop protocols for the management of emergency situations is obvious.

The heart of the 191-page book is found in the middle three sections. The first of these sections deals with general medical problems such as abdominal pain, respiratory failure, vaginal bleeding, and so forth—24 in all—but it does not discuss specific disease entities. It is aimed at stabilizing patients who have become acutely ill or who have sustained trauma, but does not discuss differential diagnosis or in-depth management. There may be some topics that certain physicians, because of their medical interests or geographical location, wish were included. For instance, a physician in an outlying area in the western states might be interested in a section on animal or snake bites. This part of the book, however, is remarkably complete.

The second section deals with drug protocols. It discusses emergency medications and how they should be administered before the patient enters the hospital. There is a subsection on each drug, briefly discussing its pharmacology, indications, precautions and side effects, with special notes. Once again, because of personal preferences, the reader may have wished certain omitted drugs had been included. It is interesting to note that bretylium, a drug that is not commonly found in a prehospital emergency care setting, was included in this section; whereas digitalis was not. Digitalis may not be considered an emergency drug by the authors of this book, but other physicians might wish that this commonly used medication had been included.

A section of the book is directed toward procedures such as starting IV's, intubations and management of pneumothoraces, to name but a few. It is not the intent of the authors for these descriptions to substitute for actual field training in the use of instrumentation and minor surgical procedures. It is a helpful guide in setting up the protocols on when to apply these commonly used emergency procedures.

The book ends with an example of standing orders for telemetry-equipped emergency services taken from the protocols written for an Emergency Medical Service Board in Albuquerque, New Mexico. In the section on implementation of emergency care protocols and basic emergency care protocols there is included a recommended basic library for the well-equipped emergency room along with eleven references.

It might be helpful to have a brief chapter on physical findings that are usually, if not always, abnormal when detected, and physical findings that could be accumulated rapidly through use of the physician's hands, ears, and eyes—not necessarily requiring simple diagnostic equipment such as the stethoscope or otoscope. One area this reviewer found especially helpful was the section on neurological assessment.

A distressing lack of standardization, even attempts to standardize prehospital emergency care, throughout the United States is pointed out. This concise guideline does an excellent job showing the usefulness of protocols, giving a skeleton on which to build and tailor protocols to local areas in the United States. *Protocols for Prehospital Emergency Medical Care* should be required reading for directors of emergency care services. It will most likely become a text used in the training of paramedics and emergency medical technicians.

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CLINICAL PHARMACY AND THERAPEUTICS—Second Edition—Edited by Eric T. Herfindal, PharmD, Clinical Professor and Chairman, Division of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco; and Joseph L. Hirschman, PharmD, Associate Clinical Professor, School of Pharmacy, University of California, San Francisco; General Manager, Professional Health Research, A Division of Health Systems Institute, Burlingame, California. Williams & Wilkins, 428 E. Preston Street, Baltimore, MD (21202), 1979. 719 pages, $29.95.

This edition of *Clinical Pharmacy and Therapeutics* represents a significant expansion of the initial edition. The 50 chapters, contributed by more than 40 practicing clinical pharmacists and educators, are divided into 13 major sections: general topics, infectious disease, gastrointestinal diseases, cardiovascular disorders, respiratory diseases, endocrine and metabolic diseases, renal disease, rheumatic diseases, diseases of the blood, neurological and psychological disorders, diseases of the eye, skin diseases and neoplastic diseases. New chapters include alcoholism (well done), pediatrics, infective endocarditis, central nervous system infections, thromboembolic disease, cardiac arrhythmias, and insomnia and anxiety. Although the above additions strengthen the text, there are numerous topics left unaddressed. Major deficiencies include fluid and electrolytes, acid-base balance, glomerulonephritis, bacterial pneumonia, chronic pain, cardiogenic shock, and applied principles of clinical pharmacokinetics. Overall, chapters are well organized, generally providing an extended discussion of the disease pathophysiology and diagnosis. Unfortunately, information regarding specific therapy is at times quite general and in places dated (for example, carbamazepine use for seizure disorders is only mentioned, and there is no discussion of problems with long-term glucocorticosteroid therapy). Nevertheless, many chapters contain excellent

tables and graphs useful in summarizing information. Adequate references through 1978 are provided at the end of most chapters.

The editors state that this text is to "help prepare the pharmacy student . . . to assume a patient-oriented role in health care." *Clinical Pharmacy and Therapeutics* provides sufficient information to the student to approach this goal. I recommend it as an acceptable text for instruction of pharmacy and nursing students in applied therapeutics, recognizing its limitations. It would also be an appropriate addition to the library of most hospital pharmacies. It has little to offer practicing physicians or clinical pharmacists.

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PEDIATRIC GASTROENTEROLOGY—Case Studies—William Liebman, MD, Assistant Professor of Pediatrics, Pediatric Gastroenterology Unit, University of California, San Francisco, School of Medicine. Medical Examination Publishing Co, Inc., 969 Stewart Avenue, Garden City, NY (11530), 1980. 496 pages, $18.00 (paperback).

As the title indicates the book consists of 58 case studies of 57 different disorders of the gastrointestinal tract in children. Each case study consisted of a one- or two-page presentation of history, physical examination and pertinent laboratory data. Next comes a series of multiple choice questions about the case. The heart of the book is the next section; the correct answer to each question followed by a discussion or commentary. This commentary is referenced, usually 15 to 20 references per case study. Finally, there is an index so that readers can proceed directly to the pages where specific problems, diseases or drugs are discussed. The conditions covered in the case studies include functional bowel disease with inflammatory bowel disease, celiac disease, parasitic infections, shigella and intractable diarrhea, and the like, and represent a broad cross section of gastrointestinal illness.

The author states in the preface that he hopes the material presented will serve as a catalyst for further study in pediatric gastroenterology. If further study includes a careful perusal of the book he has succeeded very well. The book is not intended as a textbook, but for more experienced practitioners serves as a stimulating review using a format a practitioner is most familiar with, the individual patient. For the less experienced student it presents a wealth of information in the comment section that is related to a real patient as presented in the case study. The book is very readable and one quickly finds oneself reading "one more case" in a one on one match with the author until one finds oneself at the 58th case and disappointed that it is the last.

As with any single author text, there is considerable time lag between manuscript and publication, and few references are more recent than 1976, but this does not detract from the information in the commentaries. As in any situation where one tries to simulate progressive actions in the real world in print, at times the situation is contrived. Occasionally in the question section we are expected to request a test, the results of which are given in the laboratory data section, or we are left wondering until the commentary section how frequent is *often*—5 to 10 or 20 or 50 percent? Some questions are obviously included to serve as a springboard for a lively, succinct discussion in the commentary section. Rather than detract from enjoyment of the book the reviewer found it stimulated a mental dialogue with the author, stimulating him to "go one on one with the author in just one more case."

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THE OSTOMY BOOK—Living Comfortably With Colostomies, Ileostomies, and Urostomies—Barbara Dorr Mullen and Kerry Anne McGinn, RN. Bull Publishing Company, P.O. Box 208, Palo Alto, CA (94302), 1980. 236 pages, $7.95 (paperback).

In the general field of ostomies, this is the most informative book to reach the public. The authors present, in a well-organized, easily readable form, material that should prove valuable to both patients with ostomies and health care professionals.

For the patient, although the realities of living with an ostomy are clearly spelled out, the general tone of the book is optimistic and encouraging. The illustrations are well done so that even a medically unsophisticated reader can recognize the anatomical arrangement of various types of ostomies. Anecdotal experiences, which would have no place in a scientific treatise, are often cited, but these stories only add to the solid flow of facts and instructions in a book aimed primarily at laymen.

Medical professionals will also find considerable merit in *The Ostomy Book*. The comprehensive coverage, not only of the technical details of ileostomies, urostomies and colostomies but of the practical problems of day-to-day care, will undoubtedly add to the education of most physicians and allied health workers, for this is an area of medicine usually skimmed over superficially during their training. Indeed, the focus of the book on the practical aspects of ostomy care is its most important contribution.

Several of the chapters could unnecessarily alarm patients entering a hospital for a major operation. Despite the current malpractice scene, I do not believe that patients are well-served by reciting a litany of possible surgical complications. This criticism reflects a personal bias, and I fully realize that other surgeons may be more concerned about informed consent and only stop short of warning patients that upon returning from the operating room a chunk of plaster may drop off the ceiling and hit them on the head.

Certainly the chapters covering the preoperative and postoperative periods are not conducive to a patient "living comfortably"—a goal mentioned in the subtitle of the book. In these pages, hospital discomfitures and operative complications are agonizingly described and can only add to the prospective surgical patient's *jitters*. Thus we find the following:

- ". . . first visit was almost before the cock crowed in the morning;"
- ". . . write up another three dozen orders for tests;"
- "I was introduced to new forms of misery;"
- "blood . . . may form small clots;"
- "We crowded into a cold and tiny bathroom, I didn't like any part of it," and
- "If only they'd stop nagging and leave me alone."

Such comments continue on and on, discussing bladder infections, painful wounds that may take a year to heal and stitches that may pop open.

Not very reassuring. I see no reason for a patient to worry before an x-ray examination about a "fiery heat flash following the injection." I prefer the technician's calmly informing the patient before the injection that it

is normal to experience some discomfort and not to be alarmed. Nor should the patient enter the hospital thinking about "anesthetics irritate the lining of the lungs . . . also paralyze the tiny hairs of the respiratory tract." This type of information is best handled by a preoperative anesthesiologist visit after properly evaluating a patient's emotional makeup.

The point is that relatively few operations are done at university hospitals where patients give their "history to a seemingly endless stream of eager listeners" and where "it seemed like overkill as doctors poked and palpated." Moreover, although postoperative complications may develop, in my experience less than 5 percent of patients are interested in a preoperative recitation of their possible occurrence. Nor do all surgeons follow the operative regimen discussed in the book. Surely not all surgeons would agree that "five enemas and three showers" are necessary before an intestinal operation. And many surgeons, like myself, rarely use a nasogastric tube following colon operations.

A paragraph on the pros and cons of irrigating sigmoid colostomies needs clarification. Nonirrigation was popularized in Great Britain because of poor housing standards and the problems of tying up a bathroom for the hour necessary to irrigate and empty a colostomy. In our country, and now in Sweden, the advantages of irrigation, over nonirrigation and an external appliance, are well recognized.

Notwithstanding these criticisms of the two chapters preparing the patient for operation, *The Ostomy Book* is an excellent reference source for physicians, nurses, enterostomal therapists and estomates. I would recommend this book to the latter group, however, only upon recovery from their operation. With this reservation, I salute the authors for bringing us a much-needed book that could potentially benefit hundred of thousands of patients throughout the world.

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ESSENTIALS OF CLINICAL ELECTRIC RESPONSE AUDIOMETRY —W. P. R. Gibson, MD, FRCS, Consultant ENT Surgeon, The National Hospitals for Nervous Diseases, London; Foreword by R. J. Ruben, MD, Professor and Chairman, Albert Einstein College of Medicine of Yeshiva University, New York. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 232 pages, $26.00.

Dr. Gibson states in the preface of his book that its purpose is to provide a practical introduction to electric response audiometry (ERA) for otologists, audiologists and other groups who might use ERA as part of their clinical service; that is, he has written it primarily for clinicians. In my opinion, he has succeeded in accomplishing his goal. He has written the book in a clear, easy-to-read style and has organized it in a good, logical manner. The result is a book which is comprehensive but not exhaustive with unnecessary details.

Chapter 1 provides an overview of the history and development of ERA. It gives the reader not only a temporal record of the discoveries and investigations from which ERA evolved as a clinical tool, but also establishes the perspective that ERA is the result of multidiscipline interactions. The chapter also serves to introduce and define briefly the various electric responses which are elicited and recorded from man in response to acoustic stimulation.

Chapter 2 describes all the apparatus necessary for ERA. It is organized into five sections: the test environment, the stimulation apparatus, the response-recording apparatus, the apparatus necessary for calibration of the stimulation and recording equipment, and the methods for data storage. Although all the individual components are identified, and their function in ERA described, the information provided is too superficial in some instances; and in most cases it probably would not suffice to guide clinicians who are faced with the task of selecting and purchasing all the instrumentation for ERA. Unlike th other chapters, references for additional, more-detailed information are not cited in this chapter, thus perhaps making it the weakest chapter in the book.

The remaining six chapers describe the six major kinds of electric responses to acoustic stimulation which can be recorded from patients. In their order of presentation, these types of responses are (1) the late cortical response (or vertex potential), (2) the electrocochleographic responses (or cochlear microphonic, summating potential and nerve action potential), (3) the brainstem responses (or very early responses), (4) the myogenic (sonomotor) responses, (5) the contingent negative variation (CNV) response and (6) the middle latency (early cortical) responses.

Each of the six chapters is organized in generally the same manner. First, some additional history about the responses and an explanation of terminology specific to the responses are presented. A discussion of the anatomy and physiology of those parts of the auditory sensory system which are relevant to the origin or site of lesion and diagnostic use of the responses follows; however, the reader should be aware that these discussions are not in some instances up-to-date and exhaustive in content. Next, the characteristics of the responses are described in detail for a variety of stimulaing and recording conditions. These descriptions represent an excellent compilation by the author of the results of many experimental and clinical investigations and constitute one of the strongest features of the book. Instrumentation requirements which are specific to the particular responses are presented next. Although there is some occasional redundancy between this section and Chapter 2, many pieces of information which are of practical use to clinicians are included in the section. The next section which describes the actual testing procedures when applying the responses clinically is also of good practical value to clinicians. The last section discusses the actual clinical applications of the responses and the results that are obtained for various kinds of clinical populations.

The author also includes three appendices of additional information. The first appendix is a glossary of terminology, part of which is specific to ERA and the remainder is common to acoustics or electronics. Some of the definitions are very elementary and might be of only limited value, if not confusing in some instances, to the newcomer to ERA. The second appendix provides some very practical and useful information concerning calibration of the intensity of the stimuli used in ERA. The third appendix is essentially a cookbook of instructions for operating a particular brand of ERA instrumentation, the Medelec/Amplaid Mk II system. This information will be of little or no value to most readers, and its inclusion in the book must be questioned. Certainly the space taken by this appendix could have been better used by expanding the information presented in Chapter 2 on ERA instrumentation. For example, nowhere in the book is an adequate explanation presented of the relation between sampling rate of the analog-to-digital converter and the spectrum of the electric response being sampled

and averaged. Similarly, no explanation of the relation between gain of the biological amplifier system and the input voltage range and digital resolution of the analog-to-digital converter is included in the book.

Overall, this book should be of valuable assistance to anyone who has an interest in electric response audiometry or who is already using it in a clinical situation. Although it focuses primarily on the use of ERA as a means for assessing the hearing sensitivity of a patient and the integrity of his auditory sensory system, sufficient general information about the techniques used to record sensory evoked responses is included in the book to also make it useful to those who are using such techniques and responses as a means for diagnosing and evaluating neurologic disorders.

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THE VIEW IN WINTER, Reflections on Old Age—Ronald Blythe. Harcourt, Brace and Jovanovich, 757 Third Ave., New York City (10017), 1979. 270 pages, $12.95.

As we begin the decade of the 80's, more emphasis will be placed upon our aging society, not only in America but throughout the world. Economic, political and sociologic problems, as well as the health of the aged, will gain our attention and study. Ronald Blythe, an English author, historian and teacher, examines *The View in Winter, Reflections on Old Age,* in a superbly written social history published in 1979 by Harcourt, Brace, and Jovanovich. He continues with the same style as in *Akenfield* a portrait of an English village, with the participants speaking for themselves, blending their voices in stories, a pattern that reflects their town, their lives and their times. Thirty-seven people from 70 to 92 years old talk of their lives, their hopes and their wants; most of all "they want to be wanted." They do not feel themselves loved and too many people treat them with indifference and seek no contact with them. Unable to love the old, we approach them through sentiment, duty, respect, guilt or professional detachment, and with an eye toward our own eventual decline.

The talkers are a mixture of villagers, scholars, craftsmen, priests, miners, rich and poor. The book listens to them talking. All movement in the talk is backwards to youth and childhood, none is maturity remembered, and little is in the present. The journey is coming to an end when custom and instinct says one should go on. When the old say, "I simply can't go on," they are stating their major frustration, not announcing a coming to terms with death.

The author examines the relationship between middle-aged sons and daughters confronted with a decade of geriatric care and nursing. The dread of this may be so overwhelming that it eats away at the respect and affection children have for their parents, accelerated by the degree of the parents' senility. Emotional shock and resentment occur with the reveral of roles, parents abdicating their parental role, releasing themselves only to imprison the middle-aged children with their care. Even if the parent is placed in a nursing home, the children suffer with guilt and a sense of entrapment.

There is a newness to the concept of aging. Very few people formerly lived to be 70 or 80 in spite of the bibilical three score and ten. The reason old age was venerated in the past was that it was extraordinary. Now, when the full span of life becomes the norm, people may need to learn how to be aged as they once had to learn how to be an adult. The healthy elderly person must not fall into a purposeless routine as that may well lead to a falling out of all consideration from family and society.

"What does it feel like to be nearly 100 years old?", the shepherd's widow was asked. The woman, stout and sane, answers, "Well, you wake up in the morning, and you say to yourself, 'What? Still here?' And then you make the tea." Pure English, but a delight to read and indeed to reflect upon.

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BIOLOGICAL MONITORING METHODS FOR INDUSTRIAL CHEMICALS—Randall C. Baselt, PhD, Associate Professor, Department of Pathology; Director, Toxicology and Drug Analysis Laboratory, University of California Davis Medical Center, Sacramento. Biomedical Publications, P.O. Box 495, Davis, CA (95616), 1980. 301 pages, $47.00.

Biological Monitoring Methods for Industrial Chemicals is a most welcome and useful handbook for industrial hygienists, industrial toxicologists, occupational physicians and others directly involved with work-place safety. Dr. Baselt has prepared 69 information-packed summaries of the occurrences, usages, blood concentrations, metabolism, excretion, toxicities and laboratory analyses of selected industrial chemicals. The information in each summary is so well-integrated that the reader will not only learn how a given substance is measured in a given specimen, he will also gain a sense of how to interpret the results. The more critical reader will find, at the end of each summary, several references to additional sources of information.

Dr. Baselt has described the laboratory methods in detail, providing for each assay subsections on the principles of analysis, the reagents, the instrumentation conditions, the stepwise procedures, the calculation methods, and the sensitivities and limitations. He has presented and compared alternative methods and, whenever possible, has cross-referenced assays, noting, for example, that the colorimetric method for malathion exposure also serves for other organophosphates, the gas chromatographic method for benzene also may be used for other solvents, and so forth. This practical information will help the analyst select the most versatile and reliable assays for his laboratory.

In summary, *Biological Monitoring Methods for Industrial Chemicals* is a practically oriented book that should benefit health professionals of all levels of experience. It organizes a vast amount of critical information and presents it concisely and clearly. Those who are frequently queried about industrial toxicants should keep a copy of this book near the telephone.

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QUALITY AND ACCOUNTABILITY—A New Era in American Hospitals—Stanley A. Skillicorn, MD, Director of Medical Education, San Jose Hospital, San Jose, California. Editorial Consultants, Inc., 655 Sutter Street, San Francisco (94102), 1980. 144 pages, $14.00.

In this slim volume Dr. Skillicorn describes in crisp detail the widely publicized program of quality assurance that he established at the San Jose Hospital. In the introductory chapter he gives the usual rationale for integrating the many separate ways of monitoring the quality of care, and points out that his program antedated by three

years the new standard of the Joint Commission of Accreditation of Hospitals. Deficiencies in hospital care are attributed to poor performance, rarely to lack of knowledge, and often to a breakdown in a hospital system—for example, dispensing drugs. Three prerequisites for a successful quality assurance program are said to be strong commitment by the medical staff and hospital administrator, acceptance of responsibility for the program without reservation by a multidisciplinary committee and an enthusiastic chairperson who consults frequently with the quality assurance coordinator.

Chapter 2 makes clear that the entire hospital staff and all employees are a part of the program. Quality is defined "in terms of an attitude . . . that perfection can be achieved and that an error by anyone . . . is not acceptable." The program focuses on this "dynamic attitude," not the setting of criteria and standards which had much to do with the "disillusion with . . . traditional quality assurance mechanisms." "Credentialling, restriction of privileges, chart review, auditing, and education programs failed to yield results commensurate with the time and effort they required."

In Chapter 3 the author lists the multiple sources of information that are used to "indicate where the specific problems might lie"—for example, formal committee reports, informal complaints, clinical computer data and incident reports. The integration of risk management with quality assurance is well illustrated.

Chapter 4 describes the use of "generic screens" to discover a "patient condition or patient care event that might signal one or more problems in the health care system"—such as punctures or lacerations of internal organs during operations, patient falls and prophylactic antibiotics. Once "evidence of suspected or potential problems" is obtained, a "generic-screen type of audit" is used "for tracking down problems." "Instead of setting scores of criteria, as in the diagnosis and procedure audits, the number is limited, usually to no more than six. . . ." The criteria are "critical measures that could affect outcome." These audits are completed in a few hours and up to 100 have been completed in one year. Numerous examples are given of medical problems that were pursued by this method. The same method is used in analysing potential problems in hospital management or hospital systems—for example, correctness of codes on patient charts and length of time required to discharge a patient.

Two other methods are used, besides the informational audit: special studies—such as problems in maintaining the daily surgical schedule, and team evaluation of patient care units by direct observation and surveys of staff and patients.

In Chapter 5 the author lists the titles of the members of the quality control committee, which is a committee of the board of trustees. Neither the committee nor the director can take remedial action. "It was up to the appropriate medical staff committee or hospital committee or administrator." In response to legal advice, the committee does not review the activities of individual persons, only "patient care trends and group performances. . . ." Benefits of the new program are a more vital program of continuing education, inclusion of surveys of patient attitudes, formation of a committee to deal with "unacceptable behavior by physicians," and a more positive attitude toward quality assurance and accountability throughout the hospital.

The final chapter briefly alludes to the difficulties in making peer review more effective, the desirability of "involving patients more in the provision of their own care," and the need to deal with complex contemporary issues by such means as establishing a biomedical ethics committee.

This book is a worthwhile contribution to the bloated literature on quality assurance because it describes a working program that is generally regarded as a prototype that satisfies fully the new requirements of the Joint Commission on Accreditation of Hospitals. It represents the practical state of the art of quality assessment and clearly recognizes that quality assurance requires different mechanisms than the usual audit committee. Full partnership between the hospital components of care and medical care in joint responsibility is shown to be possible. Involving all employees and seeking patient opinions are also unique. The technical methods are not as new as the author proposes, but they are clearly superior to the educational audit model that has been followed for the past 15 years. Written so as to be understandable by those lacking a medical background, this book is highly recommended to anyone who has any interest in or responsibility for any aspect of hospital-wide quality assurance.

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MANUAL OF ULTRASONOGRAPHY—Kenneth J. W. Taylor, MD, PhD, FACP, Professor of Radiology, Department of Diagnostic Radiology; Paula Jacobson, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology; Carol A. Talmont, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology, and Ralph Winters, RT, RDMS, Diagnostic Sonographer, Department of Diagnostic Radiology, Yale-New Haven Hospital, New Haven, Connecticut; drawings by Caroline R. Taylor, MD. Churchill Livingstone Inc., 19 West 44th Street, New York City (10036), 1980. 211 pages, $22.50.

This little book is intended as a companion to the *Atlas of Gray Scale Ultrasonography* but it stands alone as an introduction to the basics of ultrasonography. "Basic Principles," "Instrumentation" and "Artifacts and Pitfalls" are the first three chapters, written by Dr. Taylor. The other chapters are written by the diagnostic sonographers in his department except for the chapters "Obstetrics," "The Liver" and "The Biliary Tree," on which he collaborated. The procedures are those used at the Yale-New Haven Hospital, New Haven, Connecticut.

The book establishes the groundwork in defining the modality, proceeds to elaborate on how the various ultrasound machines effect an image and deals with the mechanics of developing an ultrasound laboratory. From there the authors discuss particular areas including obstetrics, gynecology, the liver and biliary system, the pancreas, the kidney, the spleen, the adrenal glands, abscesses, neurosonography and biopsy techniques. Anticipating the kinds of information sent by a clinician in ordering a sonogram, the text helpfully describes for technologists the anatomy of the area, the function of the organ, and the appropriate laboratory studies that are used to evaluate the suspected problem. Each new medical term is clearly and appropriately explained. This is an ideal format for technologists but elementary knowledge to physicians, who can skip to the areas on scanning technique, artifacts and how they are produced, and a description of the sonographic appearances of normal and abnormal organs. The excellent sonographic photographs (white images on a black background) are accompanied by

well-labeled, adjacent line drawings that illustrate the text. The chapter on artifacts is particularly helpful, enabling the newcomer to grasp which sonographic findings are significant and which are not.

The book does not have a section on ultrasonography of the vascular system or the parathyroids, and only a scanty section on neurosonology of the newborn head, but much of the neural investigation has occurred since the book was published. Elaboration on obtaining A-mode scans of the head for midline determination suggests this technique is more useful than it is, since computerized tomography has really supplanted this test.

The book is not an encyclopedic treatise on ultrasound, and does not address itself to such intricacies as the lobar and segmental anatomy of the liver, but, in general, it is a lucid compact exposition of the basics and, as such, an appropriate tool for those who are in training, or in the initial stages of their ultrasound exposure.

Manual of Ultrasonography, as an introduction to ultrasound, is a successful, effective and well-organized volume.

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PROFILE OF THE RESIDENCY TRAINED FAMILY PHYSICIAN IN THE UNITED STATES 1970-1979—Editor: John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington School of Medicine, Seattle. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1981. 68 pages, $12.00 (paperback).

This short (68 page) report has as its goal a description of the residency-trained family practice physicians reviewed through the years 1970 to 1979. Dr. John Geyman used four sources of information, which follow the same general pattern for tracking resident graduates. The experience at the University of Minnesota, the Medical College of Virginia, the University of Washington and New York State programs, as well as the American Academy of Family Physicians, gives solid data, and serves to identify and describe the family physicians of this era. An interpretation of this material and its implications are then given as a final chapter.

The material is presented in an organized and superbly edited fashion to make it easily comparable. There are surprising similarities in the findings of the study. The persons presenting these studies are the leaders in the academic training of family practice physicians. The stated goal of describing practice patterns, perceptions and geographic distributions of residency-trained family practice physicians in the United States is achieved. The highlights of the booklet are that a majority of the physician graduates of the family practice programs are continuing to practice as family physicians, for the most part, in association with other physicians. Review of the hospital privileges of the physicians profiled has disclosed that over 90 percent have a hospital practice and have hospital privileges. Two thirds of the graduates provide obstetrical care, a third have privileges for complicated obstetrics. Two thirds participate in surgeries for major surgical procedures, and almost all include minor surgical procedures in their office practices. There is a low percentage of hospital privilege denial. There is a large participation in teaching part time. Most of the graduates of the programs surveyed felt that their training had resulted in good preparation for practice, high satisfaction with practice and gravitation to smaller nonmetropolitan areas. This indicated that family practice was reaching a goal of training doctors who will deliver care in underserved areas. There is a high retention rate of graduates of the programs in the state where the training took place.

To all doctors and other persons interested in the delivery of health care, this unique and well-designed attempt to review family practice training during the last ten years will serve as a landmark. The new specialty of family practice and the doctors that the family practice residency training programs graduate are achieving goals and objectives set by the family practice movement, and to a certain extent those set by certain legislative bodies. To anyone interested in health care policy this honest attempt to assess the impact of a new specialty on the health care delivery of the nation is helpful. This slim volume is a must in the library of any serious student of family medicine and health care.

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Santa Rosa, California

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WILLIS'S OXFORD LECTURES—Edited and Introduced by Kenneth Dewhurst, TD, DPhil, FRCPsych. Sandford Publications, Manor House, Sandford-on-Thames, Oxford OX4 4YN, England. 181 pages. Price: 9 English Pounds, limited to 750 copies.

Thomas Willis, the discoverer of the anastomosis connecting the blood vessels at the base of the brain, received his undergraduate and medical education at Oxford and set himself up in a very successful practice in London at the age of 25. He died in 1675 and was posthumously honored by being buried among England's great in Westminster Abbey.

Although he is best known for his eponymic circle and his studies in neuroanatomy, he was, in fact, widely interested in all aspects of medicine and pharmacology. This is evident from his many and important published writings, and more even from the variety of subjects of the lectures he gave at Oxford University. In addition to the breadth and depth of his clinical knowledge and the astuteness of his observations, Willis was also famous for the elegant style he used in his oral and written presentations.

Following the practice of his day, Willis gave his lectures in Latin, and we owe Professor Kenneth Dewhurst a debt of gratitude for having made the lectures available to us in a flawless translation into English.

In doing so, Professor Dewhurst has opened up the works of yet one more of the great English physicians whose lives and writings he has been publishing in the past decades. It is interesting that in addition to six books dealing with various aspects of English medicine, Professor Dewhurst has also published an excellent and insightful book on the German poet Friedrich Schiller. Schiller also had had a complete medical training and his medical and psychological writings have been translated by Dewhurst into English from the original German.

It so happens that the book here reviewed, *Thomas Willis's Oxford Lectures,* far exceeds the often too-narrow concerns of physicians; it also is a valuable addition to the libraries of the laymen whose interests include the cultural and scientific thought of 17th century England.

ILZA VEITH, PhD, DmedSci
Professor, Departments of the History of Health Sciences, and Psychiatry, Emeritus
University of California, San Francisco

in memoriam

California Medical Association

Anderson, James E., Arcadia. Died April 1, 1981, in Arcadia, aged 58. Graduate of the University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Dr. Anderson was a member of the Los Angeles County Medical Association.

Graber, Harold L., Fullerton. Died May 2, 1981, in Fullerton, aged 64. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1941. Licensed in California in 1956. Dr. Graber was a member of the Orange County Medical Association.

Green, Norman Ellis, Pacifica. Died March 12, 1981, aged 60. Graduate of the University of Nebraska College of Medicine, Omaha, 1944. Licensed in California in 1949. Dr. Green was a member of the San Mateo County Medical Society.

Lamb, Edward James, Santa Barbara. Died December 24, 1980, in Santa Barbara County, aged 81. Graduate of Tufts University Medical School, Boston, 1922. Licensed in California in 1923. Dr. Lamb was a retired member of the Medical Society of Santa Barbara County.

Marsh, Chester, Santa Rosa. Died April 17, 1981, in Santa Rosa, aged 81. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1926. Dr. Marsh was a retired member of the Sonoma County Medical Association.

Noetling, Paul R., Angels Camp. Died April 28, 1981, in Stockton, aged 80. Graduate of Harvard Medical School, Boston, 1927. Licensed in California in 1928. Dr. Noetling was a retired member of the San Joaquin County Medical Society.

Peckham, Charles Henry, Jr., Walnut Creek. Died April 21, 1981, aged 82. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1923. Licensed in California in 1960. Dr. Peckham was a retired member of the Alameda-Contra Costa Medical Association.

Schilla, Fredrick W., San Jose. Died May 2, 1981, in San Jose of cancer, aged 65. Graduate of the University of Minnesota Medical School, Minneapolis, 1941. Licensed in California in 1945. Dr. Schilla was a retired member of the Santa Clara County Medical Society.

Sprague, Charles Pelton, Redlands. Died May 3, 1981, in Redlands, aged 71. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Dr. Sprague was a member of the San Bernardino County Medical Society.

Stephens, Dennis Hugh, Visalia. Died May 16, 1981, in Visalia, aged 41. Graduate of Cornell University Medical College, New York, 1965. Licensed in California in 1966. Dr. Stephens was a member of the Tulare County Medical Society.

Stephenson, Edward S., Cupertino. Died April 14, 1981, in Claverack, New York, aged 56. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1950. Licensed in California in 1950. Dr. Stephenson was a retired member of the Santa Clara County Medical Society.

Szukalski, Joseph P., Pasadena. Died December 31, 1980, aged 80. Graduate of St. Louis University School of Medicine, 1926. Licensed in California in 1926. Dr. Szukalski was a retired member of the Los Angeles County Medical Association.

Taylor, William Alfred, Redondo Beach. Died May 13, 1981, aged 55. Graduate of Yale University School of Medicine, New Haven, 1951. Licensed in California in 1953. Dr. Taylor was a member of the Los Angeles County Medical Association.

Weiner, Morris, Los Altos. Died May 9, 1981, at Stanford University Hospital, aged 86. Graduate of the Washington University School of Medicine, St. Louis, 1919. Licensed in California in 1943. Dr. Weiner was a member of the Los Angeles County Medical Association.

Westerbeck, Murray Otto, Bakersfield. Died May 3, 1981, in Bakersfield of leukemia, aged 68. Graduate of the University of Nebraska College of Medicine, Omaha, 1938. Licensed in California in 1939. Dr. Westerbeck was an associate member of the Kern County Medical Society.

Washington State Medical Association

Gunderson, David Harold, Everett. Died March 4, 1981, of leukemia, aged 42. Graduate of Northwestern University School of Medicine, Chicago, 1964. Licensed in Washington in 1965. Dr. Gunderson was a member of the Snohomish County Medical Society.

Shaw, Ian Anthony, Seattle. Died March 9, 1981, in a boating accident in the San Juans, aged 58. Graduate of Harvard Medical School, Boston, 1948. Licensed in Washington in 1953. Dr. Shaw was a member of the King County Medical Society.

Snyder, Merle B., Chewelah. Died March 10, 1981, in Walnut Creek, California, aged 77. Graduate of the State University of Iowa College of Medicine, Iowa City, 1927. Licensed in Washington in 1929. Dr. Snyder was a retired member of the Stevens County Medical Society.

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

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Complete literature available on request from Professional Services Dept. PML.

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(Continued from Page 23)

October 29-31—**Cardiology Update—1981.** American College of Cardiology and UCSF at Quail Lodge, Carmel Valley. Thursday-Saturday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

November 6-8—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 6-8—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 11—**Acid Base Disorders.** LLU. Wednesday.

November 14—**Cardiology for the Primary Care Physician.** UCD. Saturday.

November 17-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** UCSD at San Diego (17-18) and Tijuana (19-20). Tuesday-Friday. 20 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5-7—**Advances in Heart Disease 1982.** American College of Cardiology and UCD at Fairmont Hotel, San Francisco. Saturday-Monday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 20-22—**Conference on Nephrology.** UCSD at Hilton, San Diego. Wednesday-Friday.

January 28-30—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

August 8-15—**Reproductive Endocrinology, Infertility and Contraception.** See Of Interest To All, August 8-15.

August 29-September 5—**Concepts in Infertility.** See Of Interest To All, August 29-September 5.

October 17—**Infections and Pregnancy.** UCD and March of Dimes at Sacramento. Contact: UCD.

October 26-30—**11th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

November 11-13—**Perinatology.** UCSD at Holiday Inn at Embarcadero, San Diego. Wednesday-Friday.

December 7-9—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

PEDIATRICS

September 23-24—**38th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 25-29—**Pediatric Urology.** UCD at Silverado Country Club, Napa. Friday-Tuesday.

October 2-3—**Pediatric Gastroenterology and Nutrition.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 9-11—**Blood Diseases and Cancer in Children.** STAN at Children's Hospital at Stanford. Friday-Sunday.

October 17—**Pediatric Allergy: Principles and Management.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 453-8696 or (916) 486-2690.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

December 4-6—**Kids Have Bones, Too.** UCD. Friday-Sunday.

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

PSYCHIATRY

July 26-30—**Summer Seminar, Session II.** Mental Research Institute, Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

July 31-August 1—**Innovations: New Trends in Family Therapy, Brief Therapy and Family Medicine.** Mental Research Institute at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** So. Calif. Neuropsychiatric Institute and Hawaii Psychiatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 15 hrs. Contact: Gail Waldron, MD, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

August 20-22—**Practical Medicine for the General Psychiatrist.** UCSD at Hyatt Islandia, San Diego. Thursday-Saturday.

October 24—**Psychotherapy: Office Approach for the Primary Care Physician.** UCD. Saturday.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

RADIOLOGY AND PATHOLOGY

July 18-25—**Laboratory Medicine.** USC at Kauai Surf Hotel, Kauai, Hawaii. One week. 29½ hrs. $350.

August 8-15—**Radiology.** USC at Maui Surf Hotel, Maui, Hawaii. One week. 28 hrs. $395.

August 12—**Chest Films—An Indispensable Diagnostic Tool.** LLU. Wednesday. 4 hrs.

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 29-September 5—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 24 hrs. $345.

September 5-9—**Dermatopathology.** See Medicine, September 5-9.

September 13-17—**Digital Radiography: Clinical Applications and Technical Advances.** STAN. Sunday-Thursday.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

September 25-26—**The Dematiaceous Fungi: Clinical and Laboratory Identification.** UCSF. Friday-Saturday. 7½ hrs. $125.

October 2—**Uroradiology Seminar.** Orange Co. Urological Soc. and Western Section, American Urological Assn., at South Coast Plaza Hotel, Costa Mesa. Friday. $100. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

October 8-9—**Fine Needle Aspiration of Breast and Thyroid.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. 13 hrs.

October 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. $100, before Sept. 15; $125, thereafter. Contact: Dr. Luis M. de la Maza, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

September 25-29—**Pediatric Urology.** See Pediatrics, September 25-29.

October 2—**Uroradiology Seminar.** See Radiology and Pathology, October 2.

October 2-3—**Cataract Surgery and Intraocular Lenses Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

October 3-10—**Introductory Seminar on Operative Arthroscopy.** UCLA at Maui. One week.

October 9-10—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $225.

October 11-16—**American College of Surgeons—67th Annual Clinical Congress.** Fairmont and Hilton Hotels, San Francisco. Sunday-Friday. Contact: Fred C. Spillman, Convention Mgr., ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 15-17—**Hip Replacement.** UCLA. Thursday-Saturday.

October 16-17—**Fracture Bracing Workshops.** USC at University Hilton, Los Angeles. Friday-Saturday. 17 hrs. $375.

November 11-15—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** Institute for Medical Education and Research at Silverado County Club, Napa. Wednesday-Sunday. 20 hrs. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

November 12-14—**Techniques in Urinary Tract Surgery.** American Urological Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611.

December 2-4—**Corneal and Refractive Surgery—An Up-to-Date Evaluation.** UCSF. Wednesday-Friday.

December 3-6—**Bone Grafting: Biology and Application.** Plastic Surgery Research Foundation at Hyatt Islandia, San Diego. Thursday-Sunday. 17 hrs. $275. Contact: Jack C. Fisher, MD, P.O. Box 33387, San Diego 92103.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**4th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 25-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Monday-Thursday.

OF INTEREST TO ALL PHYSICIANS

August 1—**Herpes.** UCLA at Memorial Hospital, Long Beach. Saturday.

August 8-15—**Reproductive Endocrinology, Infertility and Contraception—3rd Annual Course.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 21½ hrs. $325.

August 15-26—**24th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui. 12 days. 37 hrs. $375.

August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

August 29—**The Medical Applications of Exercise.** UCD at El Rancho Racquet Club, Sacramento. Saturday.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** Calif. Society of Anesthesiologists at Stanford Univ. Medical Center. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-September 5—**Concepts in Infertility—1981—Fifth Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: Frank De Llyls, Astra Tours and Travel, 10929 Weyburn Ave., Los Angeles 90024. (213) 479-4444.

August 30-31—**Orthopedics for the Primary Care Physician.** UCLA at Newporter Inn, Newport Beach. Sunday-Monday.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

September 19-20—**Eating Disorders.** UCLA. Saturday-Sunday.

September 21-23—**Spectrum of Recovery: From Conception Through the Golden Years.** Scripps Memorial Hospital, Alcoholism Treatment Center, at Islandia Hyatt, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+ hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 3—**2nd Annual Hyperbaric Symposium.** Sutter Community Hospitals at Holidome, Sacramento. Saturday. 7 hrs. Contact: Kristie Grieves, (916) 454-2222, ext. 1673.

October 12-14—**Interpretative Enzymology.** UCSD at Sheraton Airport Hotel, San Diego. Monday-Wednesday.

October 12-16—**Clinical Update.** American Medical Assn. at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Dept. of Meeting Services, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 14-15—**Alcoholism and the Family.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Wednesday-Thursday. 12 hrs. $85.

October 16—**2nd Annual Neurosciences Symposium: Current Concepts for Non-Neurologists.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

October 18-21—**Sports Medicine Today.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Wednesday.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 19-22—**British Medical Association Congress.** Town and Country Hotel, San Diego. Monday-Thursday. 10 hrs. through UCSD. Contact: Mr. G. Denney, Assoc. Exec. Dir., San Diego Co. Med. Soc., 3702 Ruffin Rd., San Diego 92123. (714) 565-8888.

October 24—**Psychotherapy: Office Approach for the Primary Care Physician.** UCD. Saturday.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

November 1-5—**American Public Health Association—109th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Thursday. Contact: APHA, 1015 15th St., NW, Washington DC 20005.

November 1-6—**American Congress of Rehabilitation Medicine and American Academy of Physical Medicine and Rehabilitation.** Town and Country, San Diego. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., 30 N. Michigan Ave., Suite 922, Chicago 60602. (312) 236-9512.

November 2-6—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

November 2-6—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $325.

November 15—**Dilemmas With Drugs in Clinical Practice.** Granada Hills Community Hospital and UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

January 31-February 6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. One week.

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Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

IDAHO

July 22-25—**89th Annual Meeting of the Idaho Medical Association.** Sun Valley. Wednesday-Saturday. Contact: Idaho Medical Association, PO Box 2668, Boise, ID 83701. (208) 344-7888.

August 27-29—**Panhandle Emergency Medicine Conference II—5th Annual Scientific Session of the Idaho Chapter, American College of Emergency Physicians.** Coeur d'Alene. Thursday-Saturday. 12 hrs. Fee: $50-$115. Contact: Michael S. Carlson, MD, 3513 Pinehill Place, Coeur d'Alene, ID 83814. (208) 667-1771.

MONTANA

October 1-3—**Annual Meeting of the Montana Medical Association.** Butte. Thursday-Saturday. Copper King Inn. Contact: Montana Medical Association, 2020 11th Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 20-23—**Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 18 credit hours, also AAFP Prescribed. Contact: Convention Director, PO Box 456, Sunland Park, NM 88063. (505) 247-0539.

July 22-25—**Current Concepts in the Surgical Pathology of the Thyroid, Parathyroid, Thymus and Mediastinum.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton. 14 credit hours. Contact: W. J. Levy, MD, Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502. (505) 982-1911.

July 24-25—**Tenth Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Saturday. The Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Richard D. Lueker, MD, 201 Cedar SE, Albuquerque, NM 87106. (505) 293-9653.

July 30-August 1—**General Surgical Update '81.** Albuquerque. Thursday-Saturday. Classic Hotel. 15 credit hours. Contact: Office of CME, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

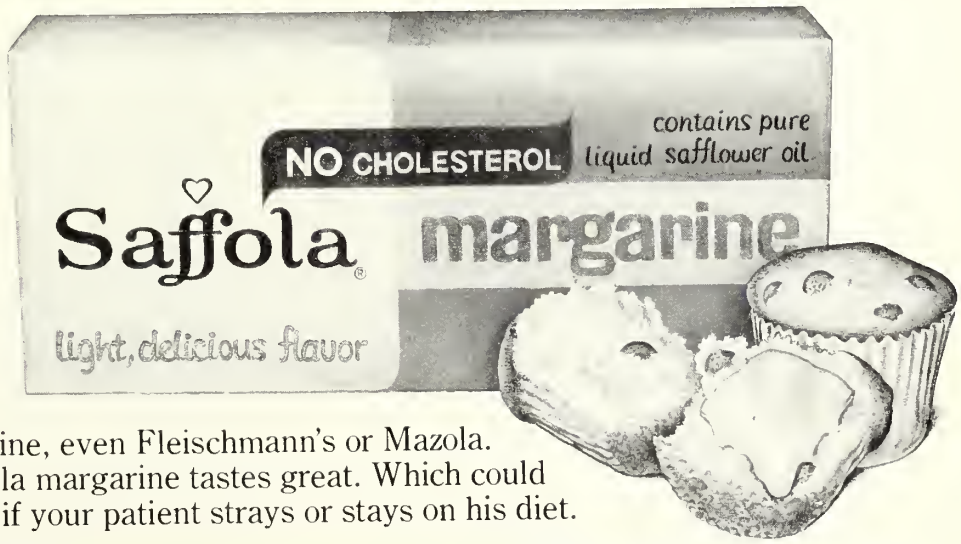
August 5-8—**Radiology for FP's—An Update.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton Inn. 16 credit hours, also AAFP Prescribed. Contact: W. J. Levy, MD, Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502. (505) 982-1911.

September 3-5—**Sports Medicine.** Albuquerque. Thursday-Saturday. Location to be announced. 10 credit hours. Contact: Otto Appenzeller, MD, Dept. of Neurology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3342.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

November 6—**Los Alamos Council for Cancer Annual Symposium for Colon Cancer.** Los Alamos. Friday. 16 credit hours. Contact: Philip H. Newman, MD, FACS, Los Alamos Surgical Associates Ltd., Los Alamos, NM 87544. (505) 662-3383.

Cheer up a low cholesterol diet with Saffola.



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But because Saffola margarine tastes great. Which could mean the difference if your patient strays or stays on his diet.

Absolutely no cholesterol and higher in beneficial polyunsaturates.

November 13-14—**Interium Meeting, New Mexico Medical Society.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Scientific Program to be announced. Contact: New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 17-21—**The Grand Canyon Conference on the Treatment of Addictive Behaviors.** South Rim of Grand Canyon. Tuesday-Saturday. Grand Canyon National Park Lodges. Hour for hour credit. Contact: T. P. Bouble, Conference Coordinator, Division of Continuing Education & Commity Services, University of New Mexico, Albuquerque, NM 87131. (505) 277-2931.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (503) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Fifth Annual Pacific NW Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

OPHTHALMOLOGY

October 1-2—**Vitrectomy.** Thursday-Saturday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

SURGERY

July 23-25—**Plastic Surgery for the General Surgeon.** Thursday-Friday. Thunderbird at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

November 20—**Soft Tissue Surgery Techniques.** Friday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

September 11-12—**Gastroenterology: Current Concepts in Colon Disorders, Hepatitis and Obstructive Jaundice.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

September 25—**Second Annual Poisoning & Toxicological Emergencies Conference.** Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

November 12-13—**Symposium on Critical Care Medicine.** Thursday-Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

December 4-5—**Urology for the Non-Urologist.** Friday-Saturday. Red Lion-Downtown, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland OR 97201. (503) 225-8700.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

July 24-26—**Washington State Society of Anesthesiologists: Seafair III Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center, Hospital Auditorium. Contact: VMMC.

July 27-31—**Psychiatry & The Behavioral Sciences: The 1980s.** Bayshore Inn. Vancouver, British Columbia. Monday-Wednesday and Friday. Contact: U/W School of Medicine.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Radiology.** Friday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

September 18—**Progress in Breast Cancer.** Seattle. Friday. Providence Medical Center. Contact: Evelyn Foote, Physician Education, Providence Medical Center, 500 17th Avenue C-34008, Seattle, WA 98124. (206) 326-5555.

September 25-26—**Annual Scientific Program.** Washington State Medical Association Annual Meeting. Friday-Saturday. Davenport Hotel, Sopkane, WA. Contact: Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801, or in-state toll-free at 1-800-552-0612.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

July 31-August 6

SPONSOR: University of Utah
TITLE: **Radiology 3rd Annual Postgraduate Course**
LOCATION: Inside Passage, Alaska
FEE: $300.00
CREDIT: 28 hours
CONTACT: Ann Osborn, MD (801) 581-7552

September 3-5

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

September 9-11

SPONSOR: University of Utah/Utah State Medical Association
TITLE: **Annual Scientific Session**
LOCATION: Hotel Utah, Salt Lake City
FEE: $50.00
CREDIT: 12 hours
CONTACT: Maxcine Fry (801) 355-7477

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 26-30, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 23-26, 1981, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 22-26, 1981, Americana Snow King Hotel, Jackson.

October 9

SPONSOR: University of Utah
TITLE: **Regional Joint ACP-ASIM Meeting Topics in Pharmacology**
LOCATION: Salt Lake Hilton
FEE: $20.00
CREDIT: To be announced
CONTACT: Gregory A. Schwitzer, MD (801) 581-7818

October 16-27

SPONSOR: Washington University School of Medicine/ Utah State Medical Association
TITLE: **Western Mediterranean Air/Sea Cruise and Medical Seminar**
LOCATION: Portugal, Morocco, Gilbraltar, Spain, Italy, France
FEE: $250.00 (medical seminar registration only)
CREDIT: 27 hours
CONTACT: Maxcine Fry (801) 355-7477

November 6

SPONSOR: LDS Hospital
TITLE: **Postgraduate Course—Renal/Pulmonary Syndromes**
LOCATION: Hotel Utah, Salt Lake City
FEE: To be announced
CREDIT: To be announced
CONTACT: C. DuWayne Schmidt, MD (801) 350-1813

November 13-14

SPONSOR: University of Utah
TITLE: **Advanced Trauma Life Support**
LOCATION: Tri-Arc Travelodge, Salt Lake City
FEE: $300.00
CREDIT: 17 hours
CONTACT: Tricia Neilson, RN (801) 533-6435

January 16-20, 1982

SPONSOR: University of Utah
TITLE: **Immune Consequences of Thermal and Traumatic Injury**
LOCATION: Snowbird
FEE: $200-$225
CREDIT: 19 hours
CONTACT: John L. Ninnemann, PhD (801) 581-7617

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

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★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

11H92-021 810717RELMAN**ASO1*
ARNOLD S RELMAN MD EDITOR *
THE NEW ENGLAND JOURNAL *
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BOSTON

UNPARALLELED PROOF OF NIGHT-LONG EFFICACY

ONLY DALMANE® C IV

flurazepam HCl/Roche

IS SIGNIFICANTLY EFFECTIVE AGAINST THE MAJOR FORMS OF INSOMNIA WITH NO WORSENING OF SLEEP ON DISCONTINUATION

Because subjective reports of insomnia and subsequent experience with sleep medication do not adequately substantiate either the validity of the complaints or the efficacy of medication, the sleep laboratory has become a valuable tool to do both. It is here that Dalmane has been objectively tested and proven effective.

Patients with objectively validated insomnia—difficulty in falling asleep, staying asleep, or both—received Dalmane 30 mg for up to 28 consecutive nights with no increase in dosage and no significant decrease in efficacy. And, upon discontinuation of Dalmane, there was no worsening of sleep past baseline levels on any parameter.[1-3]

Since insomnia is often transient, therapy for as long as 4 weeks should be given only after careful assessment of patient need with special attention to periodic blood counts and liver and kidney function tests.

Advise patients who ingest alcoholic beverages or other CNS depressants against doing so while on Dalmane therapy.

Patients should also be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle after ingesting the drug.

OM THE START
ep within 17 minutes,
average[4]
THROUGH THE NIGHT
With fewer awakenings[4]
AWAKENING
ter a 7 to 8 hour sleep,
average[4]
ROCHE®
Please see summary of product information on the following page.

THE STANDARD FOR HYPNOTIC EFFICACY WITH IMPORTANT ADDED BENEFITS

- Well tolerated[4]
- Does not significantly influence the results of many commonly ordered laboratory tests, including triglycerides, uric acid, glucose, SGOT, alkaline phosphatase and total protein[5,6] (See adverse reactions section of complete product information.)
- Compatible with chronic warfarin therapy; no unacceptable fluctuation in prothrombin time reported[7,8]

UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane (flurazepam HCl/Roche) does not cause worsening of sleep beyond baseline levels upon discontinuation.[13]

EFFECTIVE ALL NIGHT SLEEP-SPECIFIC

DALMANE® C IV

flurazepam HCl/Roche

One 15-mg capsule *h.s.*–recommended initial dosage for elderly or debilitated patients.
One 30-mg capsule *h.s.*–usual adult dosage
(15 mg may suffice in some patients).

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane (flurazepam HCl/Roche), a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies, or with impaired renal or hepatic function. Periodic blood counts and liver and kidney function tests are advised during repeated therapy.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients.
Elderly or debilitated patients: 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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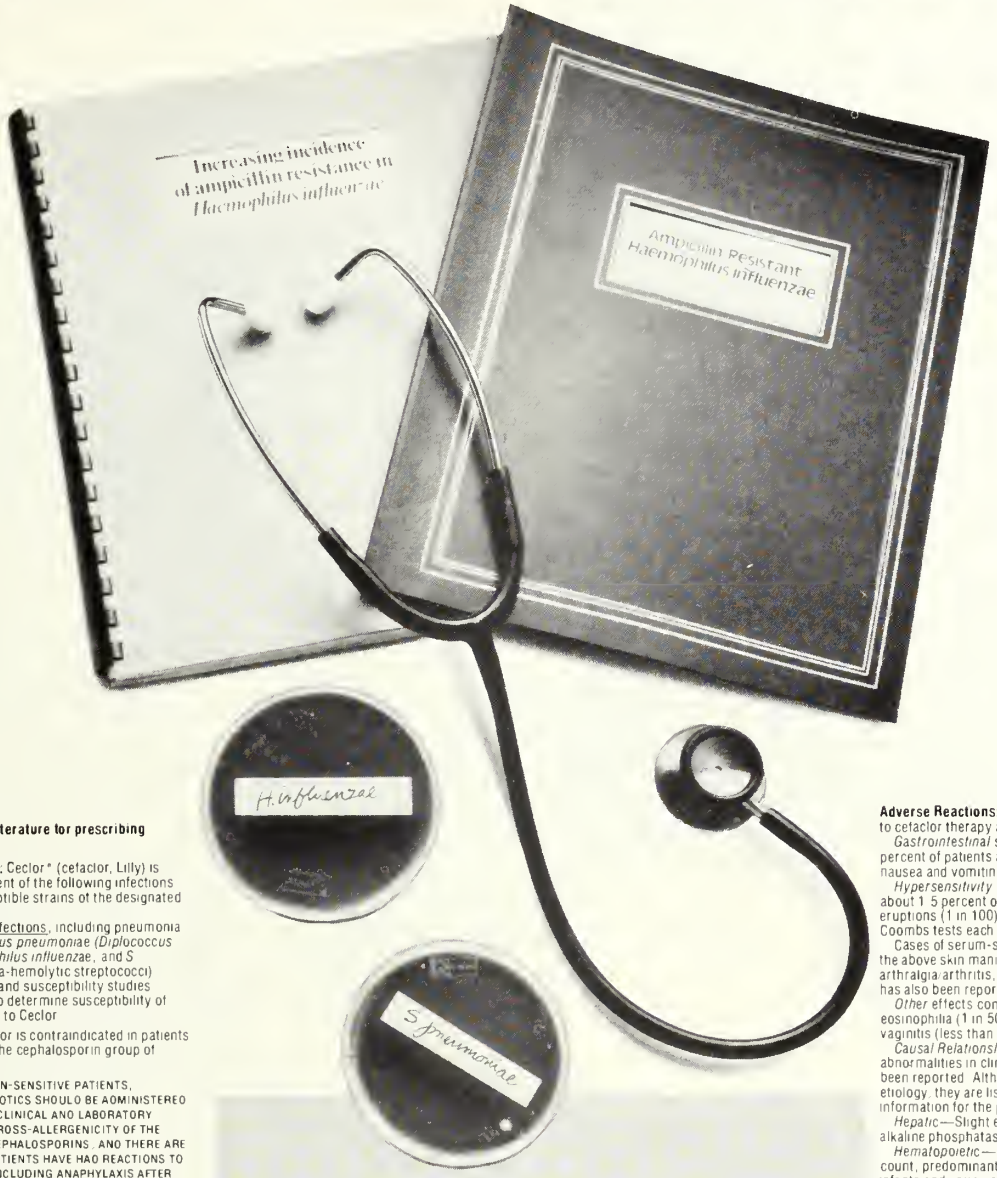

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms.

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE).

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established.

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients.

Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported. Anaphylaxis has also been reported.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [103080R]

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor
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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.

Note: Ceclor* (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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8. Principles and Practice of Infectious Diseases (edited by G.L. Mandell, R.G. Douglas, Jr., and J.E. Bennett), p. 487. New York: John Wiley & Sons, 1979.

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms o anxiety or anxiety associated with depressive symptoms Anxiety or tension associated wit stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i e., more than 4 months, has not been assessed by system atic clinical studies Reassess periodically usefulness of the drug for the individual patient

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses As with all CNS acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tol erance for alcohol and other CNS depressants

Physical and Psychological Dependence Withdrawal symptoms like those noted with barb turates and alcohol have occurred following abrupt discontinuance of benzodiazepine (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating) Addic tion-prone individuals, e.g drug addicts and alcoholics, should be under careful surveillanc when on benzodiazepines because of their predisposition to habituation and dependence Withdrawal symptoms have also been reported following abrupt discontinuance of benzod azepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid ove sedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent ma result in symptoms like those being treated anxiety, agitation, irritability, tension, insomnia an occasional convulsions Observe usual precautions with impaired renal or hepatic functio Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepa has not been shown of significant benefit in treating gastrointestinal or cardiovascular comp nent Esophageal dilation occurred in rats treated with lorazepam for more than 1 year 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeut dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 month of first observation. Clinical significance is unknown; but use of lorazepam for prolonge periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have ha elevations of LDH. As with other benzodiazepines periodic blood counts and liver function tes are recommended during long-term therapy

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressa effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY Reproductive studies were performed in mice, rats, and 2 strains of rabbi Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschis malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship dosage Although all these anomalies were not present in the concurrent control group, th have been reported to occur randomly in historical controls At 40mg/kg and higher, there w evidence of fetal resorption and increased fetal loss in rabbits which was not seen at low doses Clinical significance of these findings is not known. However, increased risk of conge tal malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam a meprobamate) during first trimester of pregnancy has been suggested in several studi Because use of these drugs is rarely a matter of urgency, use of lorazepam during this per should almost always be avoided Possibility that a woman of child-bearing potential may pregnant at institution of therapy should be considered Advise patients if they become pre nant to communicate with their physician about desirability of discontinuing the drug humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and glucuronide.

NURSING MOTHERS It is not known if oral lorazepam is excreted in human milk like oth benzodiazepines As a general rule, nursing should not be undertaken while on a drug sin many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and genera disappear on continued medication or on decreasing dose In a sample of about 3,500 anxio patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9 weakness (4 2%) and unsteadiness (3 4%) Less frequent are disorientation, depression, n sea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, e function disturbance, various gastrointestinal symptoms and autonomic manifestations. In dence of sedation and unsteadiness increased with age Small decreases in blood pressu have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents m have been taken. Manifestations of overdosage include somnolence, confusion and cor Induce vomiting and/or undertake gastric lavage followed by general supportive care, monit ing vital signs and close observation. Hypotension, though unlikely, usually may be control with Levarterenol Bitartrate Injection U.S P. Usefulness of dialysis has not been determined.

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Dosage: **Individualize for maximum beneficial effects. Increase do gradually when needed, giving higher evening dose before increasi daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosa may vary from 1 to 10mg/day in divided doses. For elderly or debi tated, initially 1-2mg/day; insomnia due to anxiety or transient situ tional stress, 2-4mg h.s.**

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Long-acting benzodiazepines have long-acting metabolites with activity which can produce excessive accumulation that may lead to unwanted sedation. Ativan® has no active metabolites, reaches steady state in 2 to 3 days and usually does not cause oversedation. Also, the shorter half-life of Ativan is consistent with b.i.d. dosage, so drug hangover is seldom a problem the next morning.

3 Not appreciably affected by aging

Unlike the long-acting benzodiazepines—diazepam ⓒ, chlordiazepoxide ⓒ, clorazepate ⓒ and prazepam ⓒ—the metabolism and clearance of Ativan are not appreciably affected by the aging process.

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Ativan® is metabolized in one simple step to an inactive glucuronide; its absorption and excretion are not significantly altered by cirrhosis or hepatitis. By contrast, the metabolism of diazepam and chlordiazepoxide has been reported to be significantly altered in patients with liver dysfunction.

See important information on following page.

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Dr. Trunkey is Professor of Surgery, University of California, San Francisco, and Chief of Surgery, San Francisco General Hospital.

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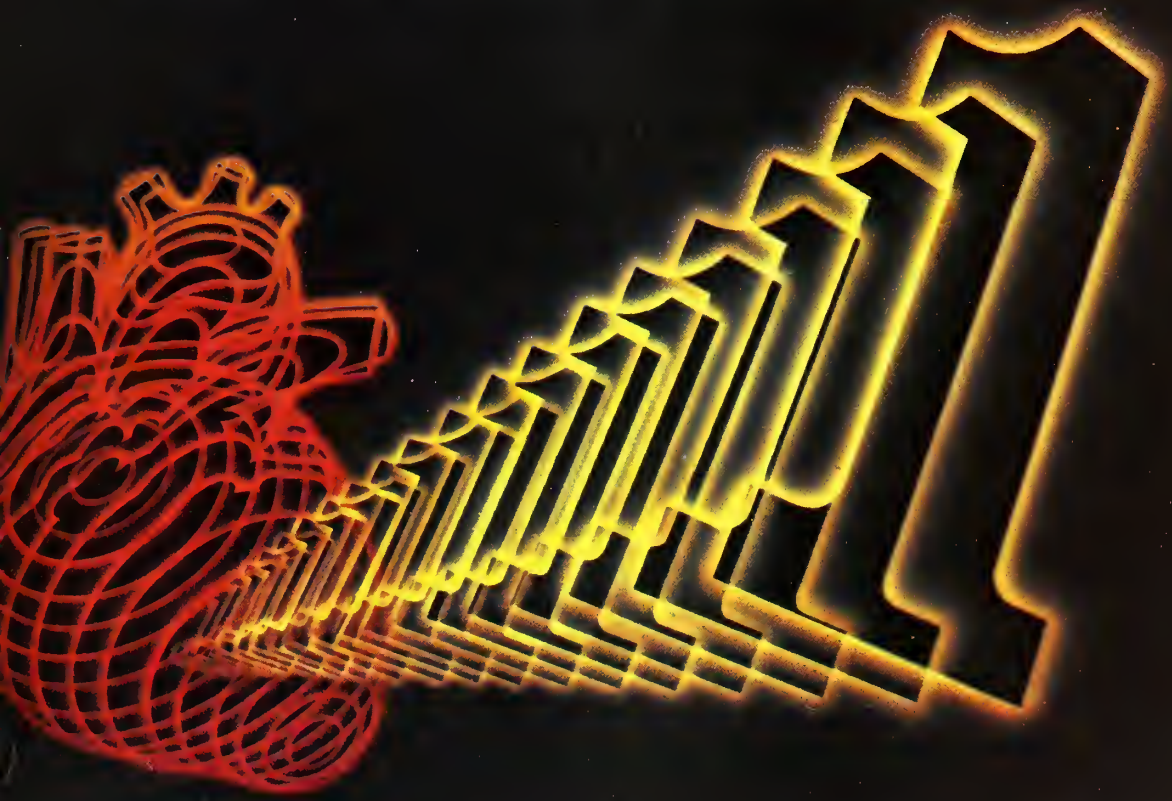
Only one beta-blocker provides once-a-day round-the-clock protection in both hypertension and angina pectoris.

CORGARD®
(nadolol tablets)
IS THE ONE



Reliable 24-hour beta blockade at all titrated dosages

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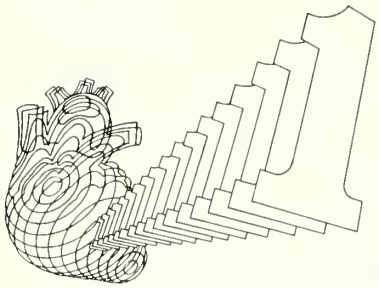
Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1[illegible] mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

SQUIBB

1981 E.R. Squibb & Sons, Inc. Issued: March 1981 511-518

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ROBERT A. BRUCE, MD
Dr. Bruce is Professor of Medicine and Co-Director of the Division of Cardiology, Department of Medicine, University of Washington, Seattle.

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★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA, ALASKA, IDAHO, MONTANA, NEW MEXICO, OREGON, UTAH, WASHINGTON (See Advertising Page 24)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

Limiting the clinical complications of serious intra-abdominal infections

Acute appendicitis

In virtually all intra-abdominal infections, there is a recurring group of three anaerobes that are seen either singly or in combination, often mixed with aerobes.

This triad, composed of *Bacteroides fragilis*, clostridia, and anaerobic cocci (particularly peptostreptococci and peptococci) may complicate perforating appendicitis, abdominal trauma, and penetrating wounds.

Complications of *B. fragilis*

Complications such as thrombophlebitis, intra-abdominal abscess, and wound dehiscence may be explained by unique virulence factors elaborated by *B.fragilis*—the anaerobe most frequently encountered in anaerobic bacteremia and intra-abdominal sepsis.

Specific virulence factors

A capsular polysaccharide on the outer membrane of *B.fragilis* appears to differentiate it from other *Bacteroides* species. Experiments in animals have demonstrated that this polysaccharide alone can cause abscess. Other virulence factors produced by *Bacteroides* are heparinase and collagenase, which contribute to thrombophlebitis and wound dehiscence. Additional virulence factors that may enhance the pathogenicity of *B.fragilis* are lipases, proteases, nucleases, β-lactamases, and superoxide dismutase.

Clinical complications: penetrating abdominal wounds

In a prospective, randomized study at Cook County Hospital, Chicago, 100 patients who had penetrating abdominal wounds with spillage of bowel contents were given kanamycin (0.5 g q12h) and either clindamycin (600 mg q6h) or cephalothin (3 g q6h).[1] The clindamycin/kanamycin-treated group showed significantly fewer episodes of septicemia or intra-abdominal sepsis (see Table 1). The higher complication rate in the cephalothin/kanamycin group was the result of infections due to

Intestinal anastomotic leak

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Acute colonic diverticulitis

anaerobic bacteria alone or a mixture of aerobes and anaerobes (see Table 2).

ne cost of morbidity

agilis was associated with complications in a majority of 335 patients with perforating appendicitis.[2] A retrospective review showed that these complications caused longer and more costly hospital stays and ter morbidity.

iting complications

tra-abdominal infections, these suggest that early, aggressive tment with an antibiotic effec- against anaerobes—especially nst *B.fragilis* with its unusual ence factors—may decrease bidity and limit potentially life- atening complications.

palli H, et al Abdominal trauma anaerobes, and ics *Surg Gynecol Obstet* 137 270-276, 1973

KS, Coll JA The continuing challenge of perforating dicitis *Surg Gynecol Obstet* 150:535-538, 1980

ext page for brief summary scribing information.

Table 1.—Septic Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Septic complications		
Septicemia	7	2
Intra-abdominal abscesses	7	3
Total complications	14	5

*Adapted from Thadepalli et al.[1]

Table 2.—Number of Anaerobe-Associated Infectious Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Mixed aerobes and anaerobes	6	0
Anaerobes	5	1
Totals	11	1

*Adapted from Thadepalli et al.[1]

†Dosage was 3 g cephalothin I.V. q6h and 0.5 g kanamycin I.M. q12h or 600 mg *Cleocin Phosphate* I.V. q6h and 0.5 g kanamycin I.M. q12h

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued (see WARNING box). A summary of prescribing information for *Cleocin Phosphate*—used in the treatment of serious infections due to anaerobic pathogens—can be found on the following page.

In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

Upjohn

Cleocin Phosphate™ STERILE SOLUTION
(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. *Musculoskeletal:* Rare instances of polyarthritis have been reported.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

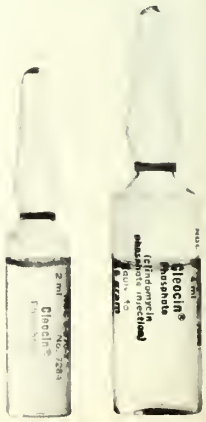
Caution. Federal law prohibits dispensing without prescription. MED B-8-9

The Upjohn Manufacturing Company
Barceloneta, Puerto Rico 00617

Upjohn

In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION
(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE



J-8809

The Research Study Club

PRESENTS

51ST ANNIVERSARY

MID-WINTER CLINICAL CONFERENCE IN

OPHTHALMOLOGY

JANUARY 24, 25, 26, 27, 1982 • HILTON HOTEL, LOS ANGELES

SUBJECTS:

- **UNDERSTANDING IMMUNOLOGY**
- **EXTERNAL EYE DISEASES**
- **UPDATE IN GLAUCOMA**
- **KERATOREFRACTIVE SURGERY**

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CLAES H. DOHLMAN, MD
Professor and Chairman
Department of Ophthalmology
Harvard Medical School, Boston

RICHARD J. SIMMONS, MD
Associate Clinical Professor of Ophthalmology
Harvard Medical School, Boston

JAMES H. ELLIOTT, MD
Professor and Chairman
Department of Ophthalmology
Vanderbilt University School of Medicine, Nashville

J. JAMES ROWSEY, MD
Associate Professor of Ophthalmology
University of Oklahoma Health Sciences Center and
Director of Corneal Services
Dean A. McGee Eye Institute, Oklahoma City

DEVRON H. CHAR, MD
Director, Ocular Oncology Unit
Associate Professor, Department of Ophthalmology
University of California and the Francis I. Proctor
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Assistant Clinical Professor of Ophthalmology
University of California
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Instructors: CROWELL BEARD, MD; JAMES L. HARGISS, MD; BERNICE BROWN, MD

Saturday, January 23, 1982, 9:00 a.m. to 5:00 p.m. & Sunday, January 24, 9:00 a.m. to 5:00 p.m.

FEE: Practicing physicians—$100 if attending Mid-Winter Course; $150 if not attending Course
Residents—$75 if attending Course; $100 if not attending Course

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Registration Deadline—January 1, 1982

Registration Fee: $200 for Practicing Physicians; $100 for Residents

Fee includes: Reception & Dinner (incl. spouses) and 3 "Round Table" lunches

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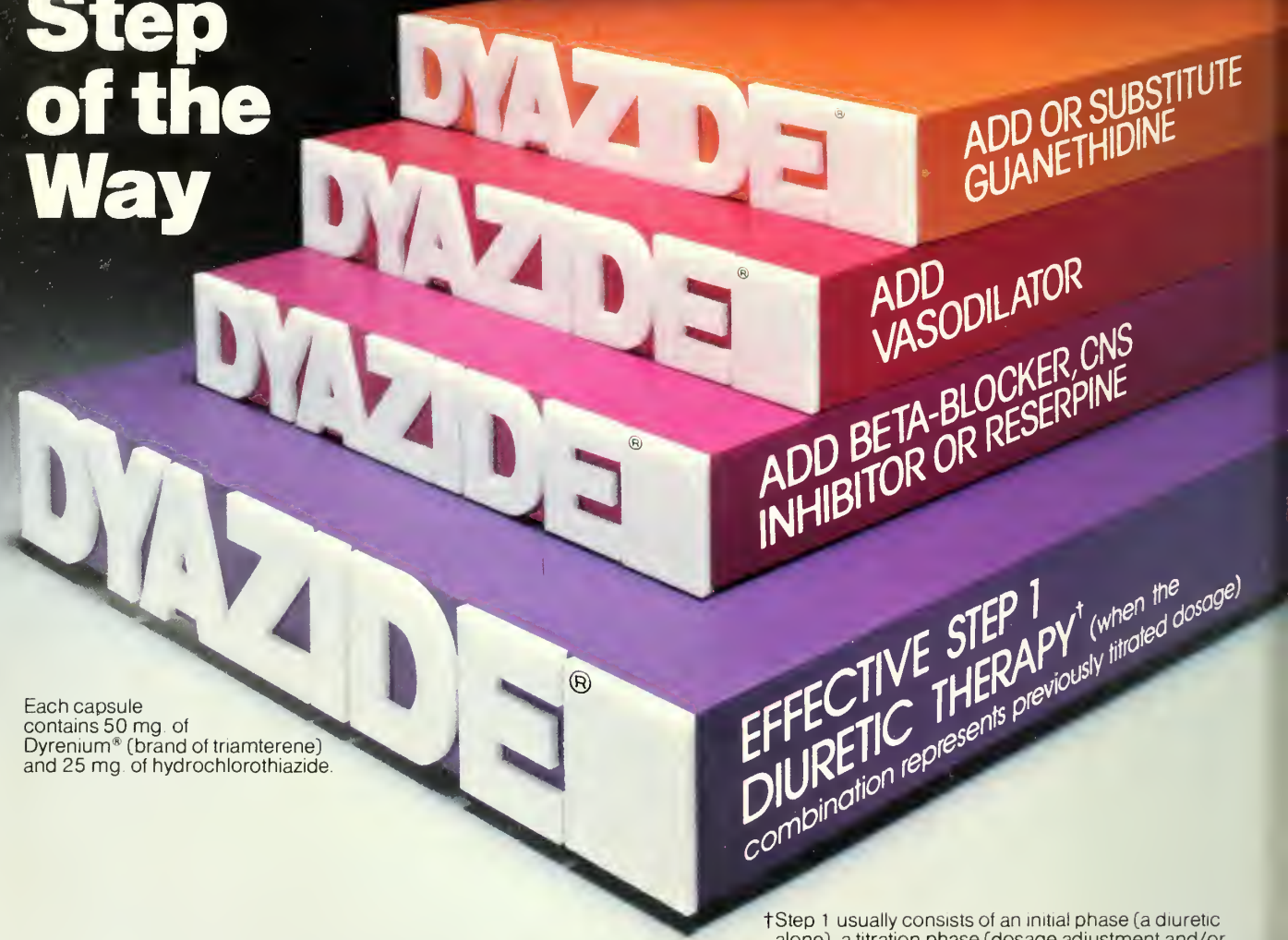
(Category I Credit 24 hours, CMA, AMA)

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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The Role of Helmets in Reducing Head Injuries From Motorcycle Accidents: A Political or Medical Issue?

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MICHAEL R. ORESKOVICH, MD, *and* C. JAMES CARRICO, MD, *Seattle*

The cases of 311 motorcycle accident victims who were seen at a major trauma center over 17 months were reviewed. The types and severity of injuries were standardized according to the Injury Severity Score (ISS) for motor vehicle accidents. Victims were categorized into groups: helmet *or* no helmet *and* major, minor *or* no head injury. *Major injury was defined as a 3 on the Abbreviated Injury Scale for "head" (loss of consciousness for at least 15 minutes with or without skull fracture and with or without neurological deficit).*

The following conclusions are drawn: (1) The death rate for those with and without helmets was not significantly different, (2) the victims of fatal accidents had identical total ISS scores regardless of the presence of helmets, (3) the chance of sustaining a severe head injury was significantly higher in the no helmet group and (4) the incidence of long-term neurological defect was three times greater in the no helmet group.

On June 10, 1967, the US Secretary of Transportation issued a number of safety standards related to the Highway Safety Act of 1966. Included was Safety Standard 3, calling for the mandatory use of helmets and eye protection for motorcyclists. During the subsequent seven years 47 states enacted legislation mandating the use of such safety equipment.[1] Because three states failed to legislate such standards the Secretary of Transportation called for the withdrawal of all highway safety funds and 10 percent of federal highway funds from the states failing to comply. Congress subsequently amended the Highway Safety Act of 1976 prohibiting the mandatory legislation of helmet laws for riders over the age of 18.[1] This was done despite a decrease in deaths per 10,000 motorcyclists from 11.5 to 5 between the years of 1966 and 1976, and in the face of numerous governmental agency and medical reports showing the efficacy of helmets in lessening the mortality and morbidity of motorcycle accidents. This congressional act resulted in the partial or total revocation of helmet laws in 29 states between the years of 1976 and 1978.[1]

The apparent reason for this sudden change in helmet legislation is political pressure from motor-

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cycle organizations and civic groups such as the American Civil Liberties Union. Their political clout stems from claims that helmets increase the frequency of certain types of injuries and that the mandatory usage of such safety devices infringes on the personal rights of motorcyclists. Because of concern about the relatively high number of serious and fatal injuries incurred by motorcyclists there have been many reports clearly disproving the claims that helmets increase the chance of a rider being injured.[2,3] To dispute the claim logically that helmets infringe on personal rights, civic minded persons offer many examples in which the mandatory use of safety goggles or hard hats for construction personnel has apparently eluded the watchful eye of those who protect our civil rights.

If there is no danger or personal infringement with the use of motorcycle helmets, it would seem absurd not to mandate the use of these devices if they truly play a major role in reducing the morbidity and mortality associated with motorcyle riding. Although there is a sizable body of reports by health organizations and governmental agencies that show a major increase in severe injuries associated with the revocation of mandatory helmet usage, medical documentation of this premise has not been adequately presented. In an attempt to add scientific credence to this already burgeoning political issue a retrospective study at a major trauma receiving center was undertaken, beginning nine months following the removal of mandatory helmet usage from statutes of the state.

Patients and Methods

Emergency room records of victims of 311 motorcycle accidents between July 1, 1978, and November 30, 1979, were reviewed. All accidents occurring during these 17 months were included. Patients were categorized according to inpatient or outpatient treatment and the presence or absence of helmets. The presence of helmets was determined by the rider's statements, the statement of the victim's family or the medic report.

In an attempt to standardize the type and severity of injury, the Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) were used.[4] Injuries to each of the six body regions were assigned numerical values according to the AIS, with the ISS equaling the sum of the squares of the AIS values for the three most severely injured body regions. The modified AIS first described by Baker was selected because of its ability to correlate varying severities of injuries in different body areas.[4] The empirical finding that the sum of the square of the AIS for the three most severely injured body regions closely correlated with mortality rates allows for the estimation of severity of injury in the multiply traumatized patient.

TABLE 1.—*Incidence of Admission to Hospital and Severity of Head Injuries for 311 Victims*

	Helmets (101)	*No Helmets (162)*	*Unknown (48)*
Hospital admission	47 (47%)	96 (59%)	..
Major head injuries	11 (11%)	51 (31%)	..
Death	4 (4%)	11 (7%)	..

TABLE 2.—*Head Injuries Among 51 Patients Without Helmets*

Cranial vault fractures	16 (2 open)
Basilar skull fractures	15
Midfacial bone fractures	12 (4 open)
Cerebral contusions	28
Brain stem contusions	16
Acute subdural or epidural hematomas	4
Others	2

Victims with AIS scores of 3 or greater for "head" were designated as severe head injuries. The minimum injuries to receive a score of 1 included cerebral concussion with or without skull fractures with loss of consciousness greater than 15 minutes; cerebral concussion with depressed or displaced skull fractures with loss of consciousness less than 15 minutes; orbital fractures and open facial fractures. The maximum score assigned to head injuries was 6, which included decapitation, medullary laceration or crush, and massively crushed skull fractures.

The severity of head injuries was ascertained by the emergency room physicians in conjunction with the appropriate surgical specialty including neurosurgery, otolaryngology and oral surgery. All patients with AIS scores of 3 or greater were admitted to the hospital.

Results

Table 1 depicts the analysis of 311 cases according to incidence of admission to hospital for victims with and without helmets and severity of head injury. Of the fatalities listed there were no pronouncements of death at the scene. All deaths occurred within the first week in hospital. There was a total of 67 patients with severe head injuries; 82 percent of these victims had not been wearing helmets. Specific head injuries are listed on Tables 2 and 3. Basilar skull fractures were documented by the presence of hemotympanum,

cerebrospinal rhinorrhea or Battle's sign. All cases of patients without central nervous system function were included in the category of severe brainstem contusions. Subdural or epidural hematomas were documented by twist drill exploration.

Injury Severity Scores for the 11 patients wearing helmets with severe head injuries ranged from 10 to 50, with an average score of 32. For those with severe head injuries without helmets the range was 9 to 66, with an average of 28.5. Among riders who sustained fatal injuries the mean ISS score with helmets was 43, while in those without helmets the mean score was 42. Tables 4 and 5 list the injuries among the 11 patients who died along with the AIS score for each injury and the overall ISS score.

There were 48 patients in whom the presence or absence of a helmet was not determined. Of the 9 patients with severe head injuries in this group, 4 died. Of all riders with fatal injuries, only one had not sustained a major head injury. In this patient there was a transection of the thoracic aorta. There was one documented cervical spine injury among those wearing helmets and four among those without helmets.

TABLE 3.—*Head Injuries Among 11 of the Patients With Helmets*

Skull fractures	3
Basilar skull fractures	2
Facial bone fractures	0
Cerebral contusions	4
Frontal lobe contusion	1
Brain stem contusion	6
Acute subdural or epidural hematomas	0
Severe facial lacerations	0

TABLE 4.—*Injuries in the 11 Riders Not Wearing Helmets Who Died*

Injuries	*AIS Number*	*Overall ISS**
Brain stem contusion, Skull fracture	5 (head)	34
Closed femur fracture	2 (extremity)	
Brain stem contusion	5 (head)	
Hemoperitoneum	4 (abdomen)	50
Open femur fracture	3 (extremity)	
Brain stem contusion	5 (head)	29
Closed pelvic fracture	2 (pelvis)	
Brain stem contusion, Depressed skull fracture	5 (head)	34
Renal contusion	3 (abdomen)	
Crushed skull fracture	6 (head)	45
Clavicular fracture	3 (chest)	
Brain stem contusion	5 (head)	
Hemoperitoneum	4 (abdomen)	66
Displaced cervical spine fracture	5 (neck)	
Brain stem contusion	5 (head)	
Hemothorax	3 (chest)	43
Open tibial fracture	3 (extremity)	
Brain stem contusion	5 (head)	
Hemoperitoneum	4 (abdomen)	50
Open femur and tibia-fibula fracture	3 (extremity)	
Concussion	3 (head)	
Atrial and superior vena caval tear	5 (chest)	34
Brain stem contusion, Comminuted skull fracture	5 (head)	34
Clavicular fracture	3 (chest)	
Skull fracture, Epidural hematoma	5 (head)	35
Renal contusion	3 (abdomen)	
5% body surface area burn	1 (general)	
	Average ISS=42	

AIS=Abbreviated Injury Scale
ISS=Injury Severity Score

*Less severe injuries to the head and other body areas not included.

TABLE 5.—*Injuries in the Four Riders Wearing Helmets Who Died*

Injuries	*AIS Number*	*Overall ISS**
Brain stem contusion	5 (head)	
Cervical spine fracture	3 (neck)	43
Renal contusion	3 (abdomen)	
Brain stem contusion	5 (head)	
Pneumothorax	3 (chest)	50
Hemoperitoneum	4 (abdomen)	
Depressed fracture, Brain-stem contusion	5 (head)	29
Hip dislocation	2 (extremity)	
Basilar skull fracture, Brain stem contusion	5 (head)	50
Cardiac contusion	4 (chest)	
Renal contusion	3 (abdomen)	
	Average ISS=43	

AIS=Abbreviated Injury Scale
ISS=Injury Severity Score

*Less severe injuries to the head and other body regions not included.

Comments

Analysis of these data allows the following conclusions to be drawn:

First, the mortality was not significantly different for those with or without helmets. The fatality of the accident was related to the overall severity of the body injury. These data contradict those of many earlier studies that report a three to nine[1-3,5] or greater incidence of sustaining a fatal injury if a helmet was not worn. Although our findings are inconclusive, it is difficult to refute preexisting reports showing up to 48 percent[6] increase in fatal motorcycle accidents following the revocation of motorcycle helmet use.

Second, the vast majority of fatal accidents involve severe head injuries. Of 19 patients in this

study who died, only one did not have a head injury with an AIS score of 3 or greater. This finding recapitulates that of all preexisting studies reviewed.

Third, the chance of sustaining a severe head injury is greatly increased if the rider is not wearing a helmet. In our study the incidence of severe head injury was increased by nearly 300 percent among those without helmets.

Conclusion

In light of the these findings and many previous reports, it is difficult to conceive of a rationale for the optional usage of motorcycle helmets. At present the only apparent justification is "infringement" on personal rights. Extrapolation of this concern for individual rights, however, leads to the obvious presence of considerable infringement on the well-being of those who are forced to share the financial burden of caring for those partially or totally disabled by these severe head injuries.

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Importance of Blink Rate

THE BLINK RATE is very important when it comes to talking about tear film abnormalities. Patients who come to you complaining of irritated eyes (they say their eyes are irritated; they give you all kinds of symptoms, including the fact that they have excessive tearing) and then it's up to you to find out if it's really tearing, or is it an irritative phenomenon which gives them the impression that they have too much tearing. But in reality, it's a dry eye. So as you're talking to the patient—and if a patient, particularly a patient in the 50's, 60's or 70's, comes in and tells me they have irritated eyes, I immediately look at the blink rate. As they are talking to me and if they are not blinking very often, or if you watch them and the blink is an incomplete blink (they don't fully close the lids), it gives you a clue as to what area to ask about and what to look for.

—PETER R. LAIBSON, MD, *Philadelphia*

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Intestinal Parasites in Southeast Asian Refugees

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A survey of intestinal parasitism in 6,241 Southeast Asian refugees (3,576 males and 2,665 females) indicated that 32.9 percent of the refugees had one or more intestinal parasites. A total of 1,178 (57.3 percent) males and 878 (42.7 percent) females harbored the parasites, with helminths representing the most frequent isolate. Intestinal parasitic infections may be considered minimal public health threats in the United States because of effective hygienic practices and sanitation facilities. However, it is important to emphasize that the attack rate also will be influenced by continued health education, job activities, and diagnosis and treatment of the refugees for these parasites.

SINCE JULY OF 1979, the United States Public Health Service Hospital in San Francisco has been used as a medical screening facility for groups of Southeast Asian refugees entering the United States. Their participation in obtaining a physical examination has been voluntary. Part of the program has involved an evaluation of infectious diseases, including an examination of stool specimens for intestinal parasites.

This survey presents data obtained from screening 6,241 refugees—3,576 males and 2,665 females—for intestinal parasites between July 25, 1979, and November 30, 1980.

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Submitted, revised, March 30, 1981.

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Patients and Methods

Each of the 6,241 patients submitted a single fresh stool to the clinical microbiology laboratory for microscopic examination. Stools were concentrated by the formalin-ether method of Ritchie.[1] One slide was prepared from each specimen. Polyvinyl alcohol specimens for trichrome staining were prepared from either liquid or semiliquid stool specimens and when protozoa from a concentrate presented identification problems.[2]

Results

During the 16-month study, 2,056 of the 6,241 refugees (32.9 percent) who submitted stool specimens for parasitological analyses were found to have one or more intestinal parasites. As shown in Table 1, *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura* represented 72.3 percent of the total number of parasites observed.

Giardia lamblia was seen in 11.2 percent of the positive specimens, and *Clonorchis sinensis* was shown to be present in 8.2 percent. No attempt was made to differentiate *C sinensis* from *Opisthorchis viverrini*.

In Table 2 a comparison is made by age and sex among the refugees having one or more parasites. Refugees between birth and 40 years old had a much higher percentage of infections than adults older than 40. Both men and women between the ages of 21 and 40 showed the highest average prevalence of parasites, 38.2 percent. Males represented 57.3 percent and females 42.7 percent of the total number of refugees harboring intestinal parasites. However, 911 more males than females were examined.

Table 3 summarizes the hazards of intestinal parasites for the patients themselves and as potential public health problems.

Discussion

Although 32.9 percent of the stool specimens of the refugees were positive for one or more intestinal parasites, this probably was an inaccurate index of infection. By examining two additional specimens on subsequent days, some of the refugees with a lower density of parasites might have been identified.[3] Helminths represented 77.2 percent of the total isolates, with *A lumbricoides* the predominant organism. Even though this parasite usually produces a benign infection, the ova are particularly resistant to deleterious environmental effects and can persist within a community despite contemporary sanitation facilities.[4]

As expected, hookworm infection represented a significant number of the helminths observed. Hookworm disease can produce anemia and decreases in both hematopoietic function and protein absorption. Although adult parasites may survive for five years in a host, temperatures below 7°C destroy the viability of the released ova and thereby affect its geographic distribution. Wearing shoes is important in controlling the parasites in an endemic area with inadequate sewage disposal facilities.

Trichuriasis is coextensive with hookworm and *A lumbricoides*. In patients who are symptomatic with trichuriasis, numerous ova will be found in a direct fecal smear, whereas in an asymptomatic patient's specimen, few ova will be present after concentration. Trichuriasis poses no risk to patients except in rare instances of rectal prolapse. Viability of ova is impaired by either direct sunlight or desiccation.

It is postulated that had ancillary methods been used for obtaining clinical specimens from the refugees, more *Strongyloides stercoralis* infections would have been identified. Strongyloidiasis potentially represents one of the most serious helminthic infections, either as duodenitis or as widespread dissemination throughout many body organs in immunosuppressed patients. Although the *S ster-*

TABLE 1.—*Prevalence of Intestinal Parasites in 2,226 Southeast Asian Refugees*

Parasite	*Number Identified*	*Percent*	*Attack Rate (Percent)*	
			Male	*Female*
Nematodes				
Ascaris lumbricoides	677	30.4	46.5	53.5
Hookworm	575	25.8	58.9	41.1
Trichuris trichiura	358	16.1	54.4	45.6
Strongyloides stercoralis	101	4.5	66.7	33.3
Enterobius vermicularis	7	0.3	57.1	42.9
Cestodes				
Taenia sp	11	0.5	90.9	9.1
Hymenolepis nana	3	0.1	66.7	33.3
Trematodes				
Clonorchis sinensis (Opisthorchis viverrini)	182	8.2	70.7	29.3
Protozoa				
Giardia lamblia	247	11.2	58.0	42.0
Entamoeba hartmanni	41	1.8	45.7	54.3
Entamoeba histolytica	24	1.1	65.2	34.8
TOTAL	2,226			

coralis life cycle parallels that of hookworm, the parasite presents different control problems. From a public health aspect, autoinfection of the host and a much shorter life cycle phase in the soil may produce a higher attack rate than hookworm. *Enterobius* was the least observed helminth in this survey, probably owing to eggs adhering to anal skin and not passing in feces. Because of its ubiquitous distribution, patients with pruritus ani should be examined for *Enterobius vermicularis*.

While there is usually no pathological condition associated with *Taenia saginata* tapeworm, *Taenia solium* can produce cysticercosis. Cysticercosis results from either ingestion of *T solium* ova or through autoinfection, rather than ingestion of cysticerci in inadequately cooked pork. It may involve the central nervous system and various muscle tissues. Both species of *Taenia* are controllable within a community by adequately cooking beef and pork.

Hymenolepis nana may persist through autoinfection, particularly in children. Often it produces no pathological condition in the host and is controllable through adequate handwashing and sanitary disposal of human waste.

In some hosts *C sinensis* parasitism may produce significant disease such as cirrhosis of the liver and intermittent cholestasis. It remains a serious medical problem for patients, owing to the parasites' long life and poor response to treatment. *Clonorchis* should not pose a significant public health problem in the United States because of its inability to complete its life cycle.

Giardia lamblia was the most frequently observed protozoan parasite. Giardiasis produces diarrhea and other intestinal upsets and impairs the host's absorptive function—which results in the malabsorption syndrome.[5] In children *G lamblia* can cause chronic malabsorption.[6] Giardiasis is present as a zoonosis in various areas and can be isolated from feces of dogs, cats and cattle. *G lamblia* cysts can resist chlorination and have been observed in community water supplies.[7] This enables the parasite to persist in the environment as a reservoir of infection. The potential impact of introducing infected refugees with giardiasis into a community may be significant unless these persons are identified and treated.

Entamoeba hartmanni is included with *Entamoeba histolytica* as a pathogenic intestinal parasite because confusion exists as to the virulence of *E hartmanni*.[8] Both protozoa were observed in 2.9 percent of the patients, none of whom showed extraintestinal manifestations. *E histolytica* produces either a symptomatic infection or an asymptomatic colonization, and contamination of water and soil with cysts of *E histolytica* in rural areas may prove hazardous.

TABLE 2.—*Comparison by Age and Sex of Southeast Asian Refugees Harboring Parasites*

Age (Years)	*Number of Males(%)*	*Number of Females(%)*	*Attack Rate by Age(%)*
≤ 1-12 ..	348(29.5)	201(22.9)	549 (26.7)
13-20 ..	271(23.0)	211(24.0)	482 (23.4)
21-40 ..	431(36.6)	350(39.9)	781 (38.0)
41-54 ..	100(8.5)	66(7.5)	166 (8.0)
≥55	28(2.4)	50(5.7)	78 (3.9)
TOTAL .	1,178(57.3)	878(42.7)	2,056(100.0)

TABLE 3.—*Hazards of Intestinal Parasites to Patients and the Public*

Parasites	*Potential Complications*	*Mode of Transmission*	*Risk in the United States*
Ascaris sp	Migration, intestinal obstruction	1-2 weeks in soil before infective orally	Minimal
Hookworm	Iron deficiency anemia	3-8 days in soil before infective dermally	Minimal
Trichuris sp	Rectal prolapse	3-5 weeks in soil before infective orally	Minimal
Strongyloides sp ..	Duodenitis, disseminated form when immunosuppressed	1-2 days in soil before infective, free living in soil	Moderate
Enterobius sp	Pruritus ani	Fecal-oral route, close household contacts at risk	Moderate
Taenia sp	*T saginata* infection, nutritional deficiency, *T solium* infection, cysticeric infection	Improperly cooked beef Improperly cooked pork	Minimal Minimal
Hymenolepis sp ..	Enteritis, anemia	4 weeks in soil, fecal-oral route autoinfection	Minimal
Clonorchis sp			
Opisthorchis sp ...	Intermittent cholestasis, cirrhosis of liver	Requires proper fish and snail hosts	Minimal
Giardia sp	Malabsorption syndrome, acute diarrhea	Sexual contact, fecal-oral route	Moderate
Entamoeba sp	Colitis, hepatic abscess	Sexual contact, fecal-oral route	Moderate

Because many refugees take food-handling employment, the potential exists for food-borne spread to other community members. Stool specimen studies for *E histolytica* should be done when patients have diarrhea (with or without abdominal pain), vague abdominal discomfort, soft stool, or gross blood and mucus in stool.

Conclusion

The high prevalence of intestinal parasites among Southeast Asian refugees warrants close attention to associated morbidity and justifies screening and treatment programs. The public health hazards associated with these infections can be minimized by educating refugees about the following: sanitary disposal of human waste, thorough handwashing before eating or dispensing of food and eradication of the habit of using human excrement as a fertilizing agent. Continued health education is recommended as well.

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Difficulty in Treating Prostatitis

PROSTATITIS IS extremely difficult to cure. The literature suggests that there is perhaps a 30 percent to 50 percent cure rate with the trimethoprim-sulfamethoxazole combination. I think if you give those persons six weeks of therapy you can increase that percentage considerably. And that is certainly the course of treatment currently recommended.

—FRANK J. TAKACS, MD, *Boston*

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Atrial Flutter Associated With Acute Myocardial Infarction

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Between 1966 and 1968, 35 of 340 patients (10.3 percent) admitted to the Los Angeles County-University of Southern California Medical Center with documented myocardial infarctions were noted to have atrial flutter while being monitored in the coronary care unit. This incidence is higher than that found in most previous studies.

Patients with atrial flutter had significantly higher mortality than infarction patients without flutter (P <0.05). The increased mortality for those with flutter was apparently the result of concurrent complications and probably not because of the arrhythmia alone.

Atrial flutter recurring for more than one day was associated with further increase in mortality (P <0.02). Also, there was a higher death rate among patients with flutter who had anterior infarctions than among those with inferior infarctions, but the difference was not statistically significant.

Most patients responded to treatment with antiarrhythmic drugs, but prior digitalis therapy apparently did not prevent the onset of atrial flutter.

THE USE OF continuous electrocardiographic (ECG) monitoring systems in coronary care units has made it possible to observe and evaluate the rhythm changes associated with acute myocardial infarction (MI). Because of the acute prognostic significance of ventricular arrhythmias, attention is usually centered on this arrhythmia. Several studies have shown that supraventricular arrhythmias are a common occurrence in the setting of acute myocardial infarction and may have clinical importance.[1-4]

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The genesis and prognostic significance of supraventricular arrhythmias complicating myocardial infarctions warrants further study. Suggested causes of atrial tachycardias include congestive heart failure and cardiogenic shock, sinoatrial node ischemia and infarction, pericarditis, atrial infarction or ischemia, and vagal reflexes or increased sympathoadrenal activity.[2,5-11] Most authors feel that the supraventricular arrhythmias alone do not increase mortality but that the underlying process causing the arrhythmias may be associated with decreased survival.[1,2,4]

Few studies have been concerned specifically with the occurrence of atrial flutter in the setting of acute myocardial infarction. We have, there-

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
CPK = creatine phosphokinase
ECG = electrocardiogram
MI = myocardial infarction

fore, evaluated this arrhythmia in the coronary care unit with regard to incidence, mortality, location of infarction, time of onset and recurrence of the arrhythmia, treatment and associated complications in patients with a diagnosis of definite or probable infarction.

Patients and Materials

There were 35 patients with atrial flutter among the 340 patients with infarction admitted to the Los Angeles County-University of Southern California Medical Center, Coronary Care Unit in two years. Patients were predominantly from the lower socioeconomic population in the Los Angeles area and their admission to the unit was on a bed-available basis. The study involved 22 men and 13 women, ranging in age from 43 to 77 years and 55 to 80 years, respectively.

The diagnosis of myocardial infarction was confirmed on the basis of a characteristic history, typical ECG changes and elevated levels of serum aspartate aminotransferase and creatine phosphokinase (CPK).[12] CPK fractionation was not available during the two-year study. Congestive heart failure was diagnosed on the basis of x-ray findings (cardiomegaly, differential blood flow to the upper lobes, vascular congestion and Kerley's lines), distended neck veins, hepatomegaly, persistent rales, gallop rhythm or increased central venous pressure. Shock was evident when there was a systolic blood pressure less than 80 mm of mercury, decreased or absent peripheral pulses, cold and clammy extremities, cyanosis and oliguria.

On admission a 12-lead ECG was taken and patients were monitored by cardiac nurses using oscilloscopes at bedside and central stations with a five-lead attachment, rate alarms and tape delay loops.[13] The patients were kept at bedrest, with a low-salt diet, oxygen, sedation and diuretics administered as required. The patients were observed for a minimum of five days after admission, and longer in those cases in which the patient's condition was unstable, followed by progressive ambulation per protocol.[14]

TABLE 1.—*Time of Onset of Atrial Flutter Following Myocardial Infarction in 35 Patients*

Time of Onset (days)	*Number of Patients*		
	Those Who Lived	*Those Who Died*	*Total*
0	2	0	2
1	6	1	7
2	0	2	2
3	6	3	9
4	5	1	6
5-14	6	3	9
TOTAL	25	10	35

TABLE 2.—*Persistence of Episodes of Atrial Flutter Following Myocardial Infarction in 35 Patients*

Length of Flutter Episode	*Number of Patients With Episodes*		
	Who Lived	*Who Died*	*Total*
Minutes	3	0	3
Less than a day	7	2	9
A day	9	1	10
	19*	3*	22
One to two days	6	2	8
More than two days	0	5	5
	6*	7*	13
TOTAL	25	10	35

*$x^2 = 4.65$; $P < 0.02$.

Results

Incidence and Mortality

Of the 340 patients admitted to the coronary care unit from 1966 to 1968, 35 (10.3 percent) were noted to have episodes of atrial flutter. Ten of the 35 patients with atrial flutter died (29 percent). This is a significantly higher death rate than that for all myocardial infarction patients during the same period (15.5 percent, $P < 0.05$).

Location of Infarction

In the 35 patients with atrial flutter, 16 had anterior MI's, nine had inferior MI's and one had a posterior MI. In the remaining patients, the locations were combined or undetermined.

Of the 16 patients with anterior infarctions, 7 died (44 percent), whereas only 1 of 9 patients with inferior infarctions died (11 percent). Although this difference is not statistically significant, the tendency toward increased mortality in patients with anterior infarctions is evident.

Time of Onset

In seven patients atrial flutter developed the day after infarction, in two it occurred two days

after infarction, in nine it developed on the third day and in six it occurred on the fourth day. In two patients with no previous history of arrhythmias, the flutter was noted on admittance to hospital. In the other patients it developed between the 5th and 14th day. Table 1 shows the time of onset of flutter for the patients who lived and those who died. There was no significant difference in onset of flutter between these populations.

Persistence and Recurrence

In our series, three patients had episodes of flutter lasting only minutes. In nine they lasted for hours (but less than a day) and in ten the episodes occurred intermittently for 24 hours (see Table 2). Monitoring also showed that in eight patients the atrial flutter lasted for one to two days, in five it lasted for more than two days and in two the episodes lasted for up to 10 days. Substantially more patients in whom the flutter lasted for more than a day died than those with shorter episodes. Although patients with high CPK values tended to have a poorer prognosis, there was no significant association between high CPK values and occurrence or persistence of atrial flutter. An example of a short episode of atrial flutter is shown in Figure 1. Onset is with a premature beat, a high degree of atrioventricular (AV) block is present, and the sinus node recovery time exceeds the normal R-R interval.

Treatment

Of the 35 patients with atrial flutter, 22 were already receiving digitalis before the onset of flutter. In almost every case prior digitalis therapy had been instituted because of symptomatic congestive heart failure. When compared with the 13 patients not receiving digitalis, we found that the patients treated with this drug tended to have higher degrees of atrioventricular (AV) block and slower ventricular responses; however, these differences were not statistically significant. Seven of the ten patients who subsequently died were receiving digitalis at the time of the onset of atrial flutter. Thus, previous administration of digitalis did not significantly affect mortality.

Eight patients who were not previously treated with digitalis were given this medication at the onset of atrial flutter. Nineteen patients who were not receiving quinidine before the onset of flutter were given this medication. One patient was cardioverted and seven were treated supportively. Twelve patients had been taking either procainamide or lidocaine before the onset of atrial flutter. No adverse effects of antiarrhythmic therapy were noted in the patients with atrial flutter.

Only three of the 35 patients with atrial flutter were receiving anticoagulant drugs. One of these three subsequently died of myocardial failure. No relationship between anticoagulation and mortality was discernible.

Previous Medical Problems and Complications

Thirteen patients had diabetes mellitus and 14 had evidence of or had a history of hypertension. Six patients (one each) had a history of bleeding peptic ulcer, gout, lues, myasthenia gravis, bronchiectasis and cirrhosis. Two had had previous cerebral vascular accidents. These problems were stable at time of onset of atrial flutter. Two patients had recovered from previous myocardial infarctions.

While in hospital for acute MI, one patient had a cerebral embolism, which occurred on the eighth day of illness while the patient was in sinus rhythm; atrial flutter, however, lasted intermit-

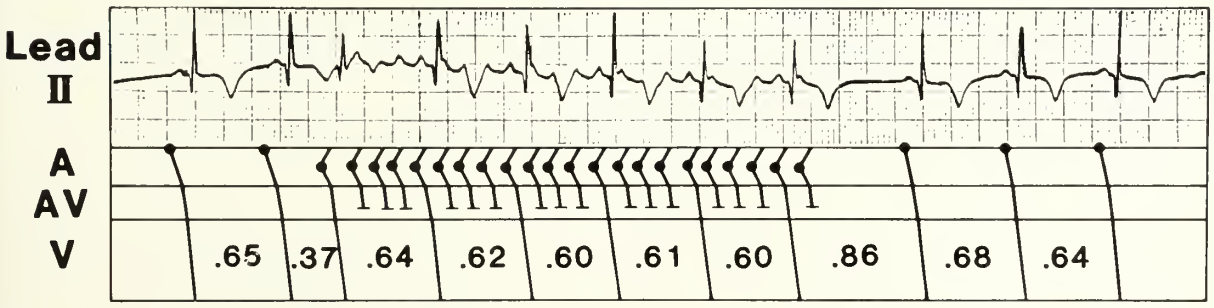

Figure 1.—Example of intermittent atrial flutter which occurred in a 55-year-old man with an inferior myocardial infarction, who had hypertension but was not receiving digitalis. The arrhythmia is initiated by a premature atrial complex, and every fourth beat is conducted to the ventricles (4-1 AV block). Spontaneous termination occurs, followed by a sinus escape interval that exceeds the normal sinus interval (860 versus 680 msec); the effective ventricular rates are similar due to the high degree of block.

tently for ten days and was treated with digitalis. Another embolic or thrombotic episode occurred on the 13th day postinfarction in this patient (see patient 5, Table 3).

Two patients had evidence of pericarditis on admission, but there were no episodes of myocardial failure or atrial infarction before the onset of atrial flutter. There was no evidence of congestive heart failure occurring secondary to the onset of atrial flutter alone, in our best judgment. Subjective shortness of breath occurred in one patient and transiently decreased blood pressure in another. There were no known recurrences after one day; if the flutter stopped for 24 hours, it did not recur.

Of the ten patients who died, autopsies were done on eight (80 percent). Recent or acute MI was found in all eight patients, with papillary muscle involvement and an intracardiac thrombus in two. Causes of death, location of infarct, and related findings are given in Table 3.

Discussion

Incidence

We confirmed 35 cases of atrial flutter associated with 340 cases of acute myocardial infarction (10.3 percent). Table 4 depicts the incidence and mortality found in other studies both before and after continuous ECG monitoring systems were developed. In the premonitoring era before 1964, the incidence of atrial flutter associated with myocardial infarction ranged from 0.5 percent to 3 percent with an average incidence of 1.2 percent (46 of 3,782 cases). In the continuously monitored patients, the incidence of atrial flutter ranged from 1 percent to 6 percent, with an average incidence of 3.2 percent (59 of 1,870 cases). The incidence in our study of 10.3 percent is higher than that in most previous reports. More recent data from our coronary care unit have shown the incidence of atrial flutter in patients with infarctions to be 6 percent.[15]

As we expected, with the advent of continuous monitoring systems, an increased incidence of documented atrial flutter was demonstrable. Comparison of our data with Askey's study[16] in the premonitored era, both of which were done at the Los Angeles County-University of Southern California Medical Center, shows almost a sevenfold increase in the incidence of documented atrial flutter. That this increase was not found with atrial fibrillation could be attributable to two main considerations.[4] First, because of its irregular rhythm and pulse deficit, atrial fibrillation has been easily diagnosed without the aid of a rhythm strip. Second, the early onset of atrial fibrillation after myocardial infarction is more easily recognized on the admission ECG than atrial flutter, when the classic "sawtooth baseline" is lacking.

Mortality

We found that 10 of 35 patients (29 percent) with atrial flutter died, while the average mor-

TABLE 3.—*Pathological Findings at Autopsy*

Patient No.	*Cause of Death*	*MI Location**	*Coronary Artery Disease†*	*Associated Findings*
1	Perforation of left ventricle, AMI	Ant, Ap, S	Circ, RCA—moderate	Multiple renal cysts, PC
2	Septal perforation, AMI	Inf, S	LAD—severe	Abdominal aortic aneurysm, splenic hematoma, PC
3	AMI	Ant, Post, S, Pap	LM, RCA—severe	Intracardiac thrombus, pericarditis, bleeding ulcer, cecal adenoma, cerebral atrophy, PC
4	AMI	Ant, Lat	LAD—severe	PC
5	AMI	Ant, Ap, S	LAD, Circ, RCA—severe	Multiple cerebral infarcts, renal artery thrombus, renal papillary necrosis, PC
6	AMI	Ant, Ap, S, Lat	LAD, Circ, RCA—moderate	PC, old contusion of right temporal lobe
7	AMI	Post, Lat, S, Pap	LAD, Circ—severe	Intracardiac thrombus, diabetes mellitus, bladder hemorrhage
8	AMI	Ant, Ap, Post, S	LAD, Circ—severe	Diabetes mellitus, PC

AMI = acute myocardial infarction; Ant = anterior; Ap = apical; S = septal; Inf = inferior; Post = posterior; Pap = papillary muscles; Circ = circumflex; RCA = right coronary artery; LAD = left anterior descending; LM = left main; MI = myocardial infarction; PC = pulmonary congestion.

*All MI's listed occurred at last hospital stay.
†Moderate = 60%-80% occlusion; Severe = 80%-100% occlusion.

tality for all myocardial infarction patients during the same period was 15.5 percent. Previous studies (Table 4) have shown death rates ranging from 0 percent to 75 percent. In studies after 1964, the mortality ranged from 0 percent to 44 percent, with an average mortality in patients with atrial flutter of 36 percent. The study by Jewitt and co-workers[17] shows no mortality associated with atrial flutter, although his small sample population precludes strong conclusions. Stock and colleagues[18] conclude that the prognostic significance of arrhythmias in the setting of myocardial infarctions can be assessed only if one takes into account the hemodynamic status of the patient. They state that in the presence of mild infarction or cardiogenic shock, arrhythmias have little prognostic significance; however, in between these extremes arrhythmias may compromise the patient's hemodynamic state, and thus affect mortality. The study by Liberthson and associates[2] indicated that there was increased mortality in patients with atrial flutter compared with patients with other atrial tachyarrhythmias, but the increase was not statistically significant. Liberthson concludes that "there was no significant difference in mortality related to the presence or absence of atrial tachyarrhythmias." Our study indicated significantly increased mortality over the general population of myocardial infarction patients ($P < 0.05$). Lown and colleagues classify all atrial tachyarrhythmias as "arrhythmias of pump failure" and they state that "patients in this group have a poor prognosis. Mortality is twice that in the rest of the population."[6] The study by Mintz and co-workers[19] in the premonitoring era also showed a statistically significant increase in the death rate associated with atrial flutter in myocardial infarction patients ($P < 0.05$). The significant increases in mortality observed in the studies by Cristal and co-workers[1] and Stock and colleagues[18] involved patients with atrial flutter and other supraventricular tachyarrhythmias and so comparisons with our data are not valid.[1,18]

Location of Infarction

Table 5 compares infarction location in the present series with that in other patients as described by other investigators. All studies show a slight predominance of anterior over inferior infarctions, but this difference was not statistically significant. Lofmark and Orinius[3] stated specifically that the infarction site for those with supraventricular tachycardia was no different than for the general MI population. James[8] has shown that

TABLE 4.—*Incidence of Atrial Flutter and Increased Mortality Associated With Myocardial Infarction in Studies Before and After Development of ECG Monitoring*

	Cases	*Flutter*	*Percent*	*All MI Percent‡*	*Flutter Percent‡*	*Increased Mortality*
Studies using ECG monitoring						
Kurland[23] (1965) ...	16	1	6.0	..	..	..
Meltzer[20] (1966) ...	141	3	2.0	..	..	..
Jewitt[17] (1967)	222	2	1.0	24.0	0.0	No
Stock[18] (1967)	200	18*	9.0	30.0	61.0*	Yes
Lown[6] (1967)	300	16	5.3	17.7	43.8	Yes
Cristal[1] (1975)	350	39†	11.0	16.0	41.0†	Yes
Liberthson[2] (1976) ..	917	29	3.0	20.5	34.5	NS
Lofmark[3] (1978)	274	8	3.0	..	..	..
Current series	340	35	10.3	15.5	29.0	Yes ($P < 0.05$)
Studies before ECG monitoring						
Master[24] (1938)	300	3	1.0	26.0	67.0	NS
Rosenbaum[26] (1941) .	208	6	3.0	33.0	66.0	NS
Mintz[19] (1947)	572	4	0.7	22.0	75.0	Yes
Askey[16] (1949)	1,247	19	1.5	51.5	63.0	NS
Goldman[27] (1950) ...	127	2	1.6	..	..	..
Ball[28] (1955)	342	7	2.0	..	..	..
Johnson[25] (1958)	187	1	0.5	..	..	..
Imperial[29] (1960) ...	153	1	0.7	..	..	..
Begg[30] (1961)	46	1	2.0	..	..	..
Julian[31] (1963)	100	2	2.0	..	..	..
Hurwitz[32] (1964)	500+	..	1.0	..	..	..

ECG = electrocardiographic; NS = not significant.

*Includes all supraventricular tachycardia except atrial fibrillation.
†Includes atrial flutter and fibrillation.
‡Mortality.

atrial arrhythmias are often associated with occlusion of the artery to the sinoatrial node, with subsequent infarction with the node. Jewitt and co-workers[17] point out that the sinoatrial node is supplied by the right coronary artery in 55 percent of cases and by the circumflex in 45 percent of cases. They go on to conclude that in patients with an anterior infarction, the development of an atrial arrhythmia indicates occlusion of a secondary major vessel in addition to the anterior descending branch of the left coronary artery; therefore, an atrial arrhythmia in the setting of an anterior infarction may herald an extension of the infarction.

Cristal and colleagues[1] state that the infarction site is an important determinant of the mechanism of the arrhythmia. They hypothesize that because of the coronary anatomy, the sinus and AV nodes can be impaired with relatively little myocardial damage in patients with inferior infarctions. Therefore, diverse supraventricular arrhythmias can be produced without adversely affecting the patient's prognosis. But with anterior infarctions, supraventricular arrhythmias are felt to arise because of myocardial failure or catecholamine excess, which are both related to poorer prognosis. They conclude that supraventricular arrhythmias portend a poorer prognosis in anterior but not inferior infarctions.[1] Our findings are in agreement with these conclusions—the death rate was four times greater in those patients with atrial flutter and anterior infarctions than in those with atrial flutter and inferior infarctions.

In their studies relating atrial fibrillation to myocardial infarction, neither Liem and co-workers[9] nor McLean and colleagues[10] found significant differences related to infarction site (Table 1).

Time of Onset

The figures from the present study on time from illness to onset of atrial flutter agree with those of Lofmark.[3] Cristal and colleagues[1] indicate that of 39 instances of atrial flutter and fibrillation, 24 (62 percent) occurred within 24 hours of admission. However, they do not report the time of onset with respect to day the infarction occurred.

Persistence and Recurrence

In the present study, those patients with more than one day of flutter had significantly higher mortality than those with shorter episodes. There are two possible explanations for this relationship. First, persistence of atrial flutter refractory to treatment may be occurring in those with more severe heart failure and larger infarcts and, hence, increased mortality. And, second, recurrent atrial flutter may have compromised the hemodynamic status of infarcted patients and, thus, be a causative factor in their increased mortality.

In our study, the persistence of atrial flutter bore no relationship to previous digitalis therapy.

Treatment

Most of the reviewed studies favor electrical cardioversion for the treatment of atrial flutter. Jewitt and co-workers[17] reported 100 percent success in converting their two patients in atrial flutter back to sinus rhythm with countershock. Meltzer and Kitchell[20] also stated that excellent results were obtained with countershock and that this is the method of choice for treatment of atrial flutter. Lown and associates[5] reported that the short-acting glycoside ouabain should be used when atrial flutter is observed, but if this arrhythmia is compromising the patient's hemodynamic status, cardioversion should be done followed by

TABLE 5.—*Location of Infarction in Patients With Atrial Flutter in Present Series and in Previous Studies*

Study	Total No. of Cases	No. of Patients With Infarcts in These Locations				
		ANT.	INF.	POST.	Combined	Undetermined
Current series	35	16	9	1	5	4
Cristal[1]	150*	60	38	..	21	35
Kurland[23]	1	0	1	0	0	0
Jewitt[17]	2	2	0	0	0	0
Lofmark[3]	8	4	1	..	..	..
McLean[10]	220†	80	70	..	..	..
Liem[9]	80†	42	34	0	4	0

ANT = anterior; INF = inferior; POST = posterior.

*Patients with supraventricular arrhythmias.
†Patients with atrial fibrillation only.

digitalis and quinidine therapy to prevent recurrence. Josephson and colleagues[21] have recommended that if these therapies fail, DC countershock should be used; it was successful in 95 percent of their cases. In the series of Liberthson and associates,[2] 20 patients with atrial flutter were treated with intravenous medications and nine were treated with DC cardioversion.

In our series, cardioversion was done in only one patient because only in this case was it felt that the persistent arrhythmia was causing hemodynamic deterioration. The other patients had either single or multiple short bursts of flutter, or intermittent flutter which did not dramatically change the hemodynamic status. Thus, pharmacologic therapy was carried out.

Haft and co-workers[22] describe three cases in which atrial flutter was terminated by rapid atrial pacing and advocate this type of cardioversion. None of the previously mentioned studies have included this method, and in recent years it has had variable acceptance as the treatment of choice for atrial flutter.

Conclusions

- The incidence of documented atrial flutter after myocardial infarction was 10.3 percent in this study and has increased with the advent of continuous monitoring systems in practically all reported studies.
- There is increased mortality for infarction patients with associated atrial flutter ($P < 0.05$), but this is primarily a result of concurrent complications and probably not because of the arrhythmia alone.
- More than two thirds of the episodes of atrial flutter began three or more days after the infarction (69 percent) in our study, and similar experience has been reported elsewhere.
- When episodes of flutter persisted for more than a day, there was a significant increase in mortality ($P < 0.02$).
- Most patients responded to antiarrhythmic drugs; DC shock for cardioversion was used effectively in one patient.
- Atrial flutter in patients with anterior infarctions may indicate a worse prognosis than in those with inferior infarctions, although this difference did not reach statistical significance in our study.

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New Noninvasive Approaches to Evaluating Coronary Heart Disease

VICTOR FROELICHER, MD:* *Coronary angiography and left ventricular angiography remain the definitive tools for the assessment of coronary heart disease. However, these invasive procedures carry the risk of catheter-induced vascular and cardiac complications and so the search for suitable noninvasive methods for examining the heart has continued. There is a need for reliable and safe techniques of evaluation in cardiac patients initially and serially both at rest and during various forms of stress.*

This conference will focus on several types of noninvasive studies in which there have been substantial advances in the past few years. Work is now being done to validate these techniques. The noninvasive techniques that will be discussed here include multiple-lead exercise testing, high resolution electrocardiography, left ventricular volume assessment by radionuclide techniques, and two-dimensional echocardiography. Certainly electrocardiography and exercise testing are not new, but there have been recent advances in them that will be presented.

Dr. Goldberger will start with the use of standard electrocardiograms for assessment of ischemia and then present his new exciting work using high frequency electrocardiography.

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Electrocardiograms in Ischemic Heart Disease†

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Basic Ischemic ECG Patterns

Patterns on electrocardiograms (ECG) seen with ischemia will vary depending on three major factors: (1) the duration of cardiac ischemia (acute versus chronic), (2) the extent of ischemic injury (subendocardial versus transmural) and (3) the location of injury (anterior versus inferior wall) (Figure 1). With classic *transmural* infarction, involving virtually the full myocardial thickness, the ECG usually shows a characteristic sequence of depolarization changes (new Q waves) and repolarization changes (ST elevations followed by T wave inversions). The Q waves reflect a regional loss of electromotive potentials. The ST segment elevations represent an epicardial *current of injury*. The precise pathophysiology of this injury current is unresolved but probably relates to a decrease in membrane resting potential and to a shortening of action potential duration.[1] Tall positive T waves (so-called hyperacute T waves) may also appear during the earlier phase of infarction. These hyperacute T waves have the same clinical significance as ST elevations. It is of note that tall positive T waves may sometimes appear without

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
HR = heart rate
LBBB = left bundle branch block
LR = likelihood ratio
LVH = left ventricular hypertrophy
WPW = Wolff-Parkinson-White (syndrome)

ST elevations as the initial sign of acute infarction (Figure 2). During the evolving (chronic) phase of acute myocardial infarction, T waves become inverted in leads previously showing ST elevations and hyperacute T waves. These ischemic T wave inversions reflect a local prolongation in repolarization time.

The temporal evolution of Q waves and ST-T changes following *transmural* myocardial infarction is also variable. In some patients, pathologic Q waves may regress in size or disappear entirely. Similarly, complete or partial resolution of ST-T changes may occur. Persistent ST segment elevation following acute myocardial infarction is a highly specific but relatively insensitive sign of underlying ventricular aneurysm.[2]

Acute transmural ischemia without infarction may occur in the setting of Prinzmetal's variant angina.[3] Patients with this syndrome show ST elevations during episodes of anginal pain. Following the ischemic attack, the ST segments return

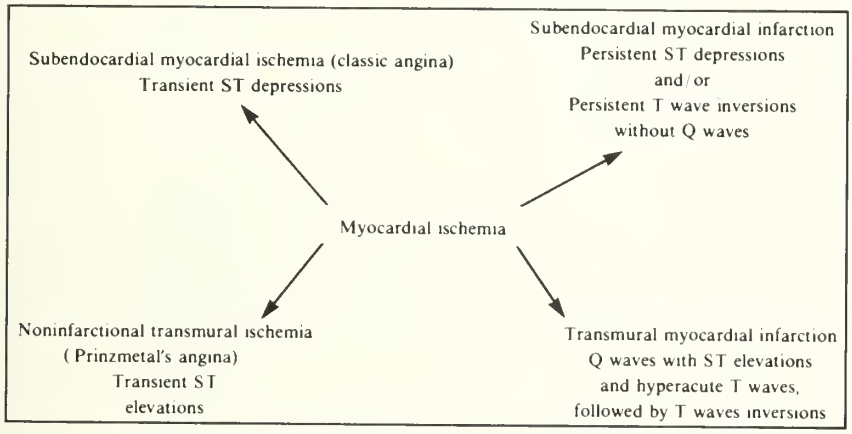

Figure 1.—Variability of electrocardiographic patterns with myocardial ischemia. (Adapted from Goldberger AL, Goldberger E: Clinical Electrocardiography, St. Louis, CV Mosby, 1977.)

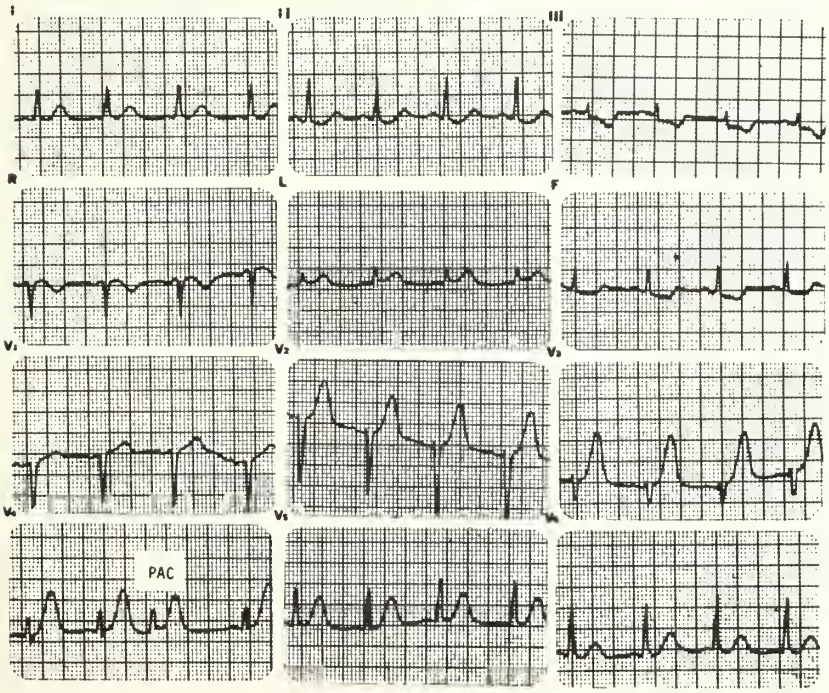

Figure 2.—Hyperacute T wave changes with anterior infarction. Note tall positive anterior T waves seen as earliest sign of acute myocardial infarction in this patient. Reciprocal inferior lead ST depression is also present. (Reprinted by permission from Goldberger AL, Goldberger E: Clinical Electrocardiography. St. Louis, CV Mosby, 1977.)

to baseline without the appearance of new Q waves. Variant angina is caused by coronary artery spasm, either with otherwise normal coronary arteries or with some underlying fixed obstructive lesion.

By contrast, patients with classic angina generally have ST depressions during episodes of ischemia. ST segment depression reflects a subendocardial current of injury, in contrast to ST segment elevation, which reflects epicardial injury. In general, the subendocardium, because of its greater hemodynamic vulnerability, is more susceptible to ischemic injury than the epicardium. ST segment depressions, due to transient subendocardial ischemia, are also the hallmark of positive (abnormal) stress electrocardiograms.

Finally, in cases of more severe ischemia, actual subendocardial infarction may occur, resulting in more persistent ST segment depressions. In other cases of nontransmural infarction, deep T wave inversions may be seen. Subendocardial infarcts involving less than half the thickness of myocardium generally do not result in new Q waves. However, more extensive nontransmural infarction may produce Q waves.[4] Therefore, the classic distinction between *transmural* and *subendocardial* (nontransmural) infarction solely on the basis of the ECG findings is an oversimplification.

In addition to the duration of ischemia and the extent of affected myocardium, the third factor affecting the ECG is the location of infarction. In simplest terms, acute infarction is usually localized to a portion of the anterior wall or inferior wall, reflecting the regional distribution of the coronary arteries. Anterior wall infarction produces primary changes in one or more of leads I, aV_L and V_1-V_6. Inferior wall injury is reflected in leads II, III and aV_F. Occasionally, infarction of the true posterior wall of the left ventricle occurs and may not produce Q waves in any of the 12 conventional leads. Instead, true posterior myocardial infarction is recognized by a reciprocal increase in R wave height in leads V_1 and V_2. Right ventricular infarction may occur and is usually associated with changes in leads II, III and aV_F.[5]

One of the key aspects of the ECG pattern of acute infarction is the reciprocal nature of the ST-T changes. For example, acute anterior infarction produces ST elevations in one or more of leads I, aV_L and V_1-V_6, and reciprocal ST depressions in the inferior leads. Similarly, with acute inferior myocardial infarction, reciprocal ST depressions are seen in the inferior leads. These reciprocal ST depressions help differentiate acute infarction from other common conditions that produce diffuse ST segment elevations, notably acute pericarditis and the normal variant early repolarization pattern.

In some cases, the ECG changes with acute ischemia or infarction may be relatively subtle or even absent. Therefore, a single ECG showing no abnormalities does not exclude acute infarction. Furthermore, in some patients with acute ischemia, *paradoxical normalization* of the ECG may be seen with angina or acute myocardial infarction.[6] In such cases, the resting ECG may show abnormal T wave inversions. Acute ischemia may cause a relative increase in T wave positivity (hyperacute changes) which paradoxically normalizes these inverted T waves (Figure 3).

Another interesting subset of patients with ischemic heart disease have deep T wave inversions in the anterior precordial leads with severe angina but do not have enzymatic evidence of acute myocardial infarction. In our experience patients with this syndrome of chest pain and noninfarctional anterior T wave inversions in three or more of leads V_1-V_4 invariably have severe stenosis of the left anterior descending coronary artery and usually show some abnormality in anterior wall motion by ventriculography (A. Goldberger, MD, D. Costello, MD, unpublished data, 1980).

Limitations of ECG Diagnosis

The uses of ECG's in diagnosing ischemic heart disease must be tempered by recognition of certain important limitations in both their sensitivity and specificity.[7] Conduction abnormalities such as left bundle branch block (LBBB) and the Wolff-Parkinson-White (WPW) syndrome may mask ischemia patterns. Similarly, left anterior hemiblock may obscure prior inferior myocardial infarction by producing small R waves in the leads II, III and aV_F.[8]

The specificity of the ECG is also limited because numerous conditions can simulate the patterns of infarction, producing Q waves, ST elevations, ST depression or tall, positive T waves.[7-9] Recognition of these ECG pseudoinfarct patterns is of particular importance to clinicians. For example, Q waves may occur in at least four settings, including (1) normal and positional variants, (2) ven-

tricular enlargement, (3) ventricular conduction abnormalities and (4) myocardial injury. Normal variant Q waves (0.04 second or longer) may occur in leads III, aV_F, V_1, V_2 and aV_L in addition, of course, to aV_R. Poor R wave progression is a common finding with left ventricular hypertrophy (LVH) and also with right ventricular enlargement (particularly with acute or chronic cor pulmonale). Deep pseudoinfarctional Q waves are an important feature of the ECG in hypertrophic cardiomyopathy. Noninfarctional QS waves in the right chest leads are common with LBBB, reflecting abnormal septal depolarization. The WPW pattern is often associated with inferior lead Q waves, due to altered ventricular activation. Finally, Q waves may occur with any type of myocardial injury, ischemic or otherwise, that results in myocardial fibrosis or replacement (for example, cardiomyopathy, amyloid or tumor).

ST segment elevations are also not pathognomonic of acute infarction. Normal variant ST elevations (early repolarization pattern) are common, particularly in the midprecordial lead in young men (Figure 4). Pericarditis also produces diffuse ST elevations. ST elevations in the right chest leads may be seen with LVH or LBBB. Similarly, ST depressions may be due to causes other than ischemia, including hyperventilation, digi-

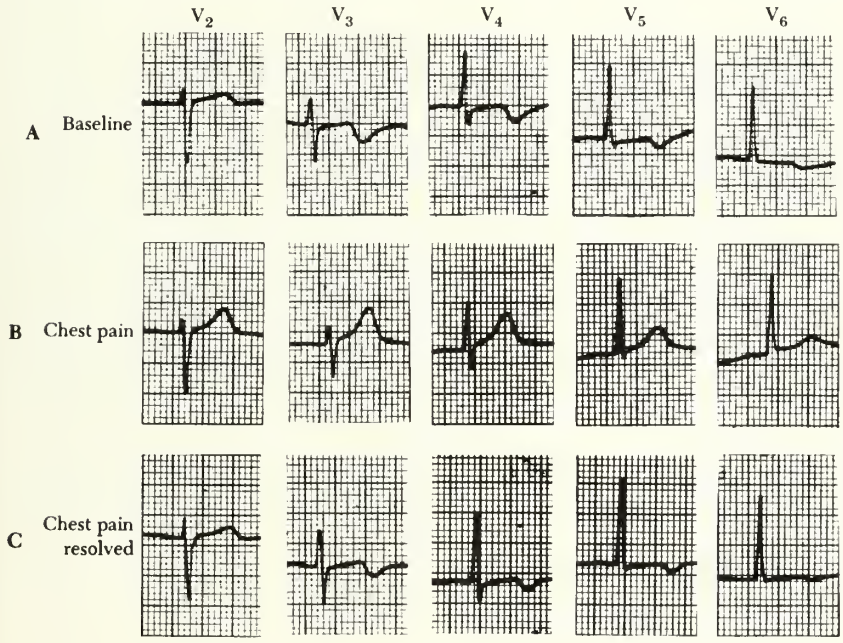

Figure 3.—Paradoxical normalization of T waves inversions. **A,** baseline electrocardiogram showing ischemic T wave inversions; **B,** during episode of angina T waves have "normalized"; **C,** following pain, T waves reverted to original appearance. (Reprinted by permission from Goldberger AL: Myocardial Infarction Electrocardiographic Differential Diagnosis, 2nd Ed. St. Louis, CV Mosby, 1979.)

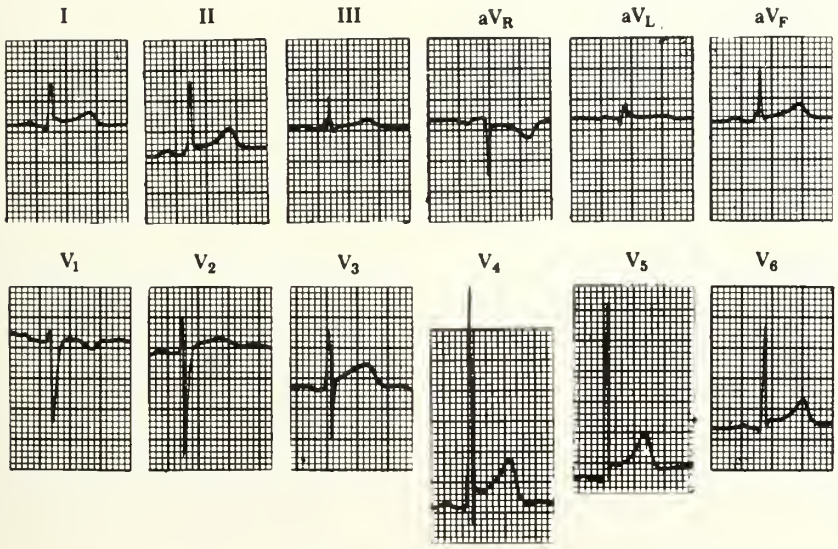

Figure 4.—Normal variant early repolarization variant. Note diffuse ST elevations most pronounced in the midprecordial leads.

talis effect, ventricular *strain,* hypokalemia and bundle branch block.

T wave changes may also occur in nonischemic settings. For example, prominent T wave inversions may be seen with cerebrovascular accidents, in particular subarachnoid hemorrhage[10] due to altered autonomic tone. Prominent T wave inversions may also occur with pericarditis, cardiomyopathy, intermittent LBBB,[11] ventricular strain, after tachyarrhythmias (posttachycardia pattern)[12] after pacing (postpacemaker T wave pattern)[13] and with mitral valve prolapse.[14] Normal variant T wave inversions may be seen on the right precordial as part of the *juvenile T wave pattern* and in the mid-left chest leads with the early repolarization variants. Finally, tall positive T waves simulating hyperacute myocardial infarction may also occur with hyperkalemia, cerebrovascular injury and in the right precordial leads with LVH or LBBB.

Because of these limitations in sensitivity and specificity, the ECG should always be interpreted in light of all available clinical information. Correlative data obtained from other noninvasive tests described in this conference may be particularly helpful in selected cases.

High Frequency Electrocardiography

To help enhance the diagnostic accuracy of ECG's, investigators have also studied *high frequency electrocardiograms.* Most of the voltage of the QRS complex is generated by relatively low frequency components; frequencies above 80 Hz make up only a small fraction of QRS potentials recorded on the surface of the body. In the past, high frequency components were measured by counting the number of notches on ECG complexes recorded at high gain with high fidelity recorders.[15,16] Such studies showed an increased number of QRS notches with ischemic heart disease and also ventricular hypertrophy.

Recently, in association with Drs. Bhargava, Froelicher and Covell at the University of California, San Diego, I have measured high frequency QRS potentials in a more quantitative way. Our studies have been carried out using a portable microcomputer system designed by David Mortara, PhD of Marquette Electronics, Milwaukee, Wisconsin. This instrument permits signal-averaging of multiple QRS complexes to reduce noise. The QRS is then passed through an 80 to 300 Hz digital filter. As shown in Figure 5 the residual high frequency QRS, recorded at very high gain (400×), has a spindle-shaped appearance. The peak of the waveform coincides with the sharp peak of the R or S waves, which make up most of the high frequency potentials. The high frequency signal can then be digitized using a computer and the effective voltage of the waveform can be measured.

Using this new technique for quantitative high frequency electrocardiography, we have found that

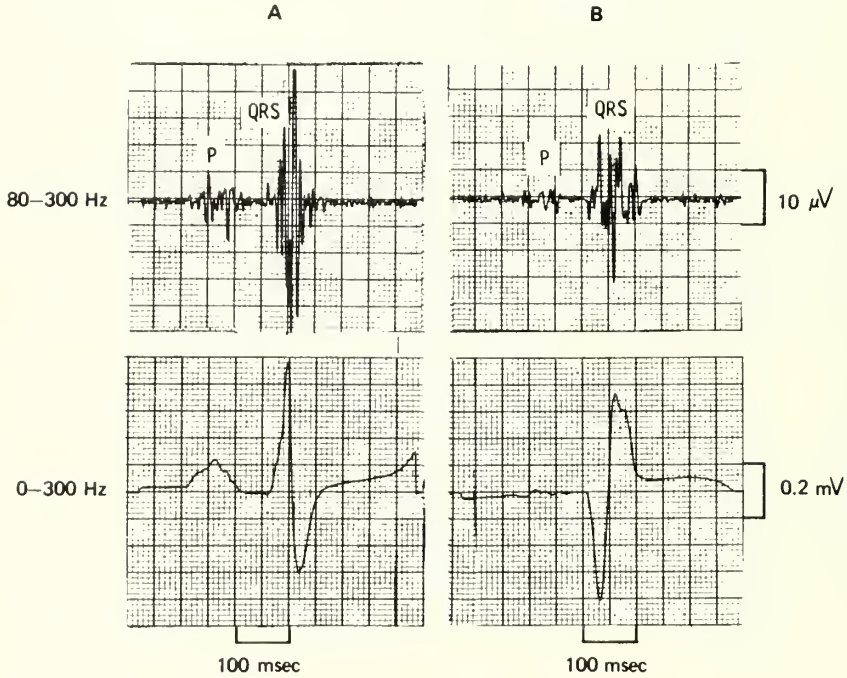

Figure 5.—High frequency electrocardiographic recordings (lead aV_F). **A**, normal subject; **B**, patient with prior inferior myocardial infarction. Lower panels show unfiltered (0-300 Hz) electrocardiogram and upper panels show electrocardiogram recorded at high gain after filtration of lower frequencies. Note relatively reduced amplitude of high frequency (80-300 Hz) signal with infarction, indicating loss of high frequency voltage.

myocardial infarction reduces total high frequency voltage.[17-19] We have also found contrary to classic ECG theory that the number of low amplitude QRS notches actually correlates inversely with total high frequency content. Reduction of high frequency voltage following myocardial infarction probably reflects an overall decrease in electromotive force and possibly also slowing of conduction. At present, studies are underway to see if such quantitative high frequency measurements can increase the diagnostic accuracy of the conventional ECG.

DR. FROELICHER: *The application of microprocessor technology to electrocardiography will lead to exciting advances in health care. The system that we have been using has the computer power of a system that 15 years ago would almost have filled a room; now it is all contained within a standard three-channel* ECG *machine. The previous use of high frequency electrocardiography was limited by problems with interference and expensive equipment. Also, it was difficult to acquire and store the signals because of the excessive signal-to-noise ratio. All these problems are circumvented with this system. Dr. Goldberger plans to continue his work with this system and evaluate surface bundle of His spikes and early repolarization.*

Dr. Tubau will next summarize his experience at the Montreal Heart Institute with the use of multiple ECG *leads during exercise testing in patients with and without previous myocardial infarction. We are very happy to have Dr. Tubau at* UCSD *as a research cardiologist in the Nuclear Medicine Department, working with Dr. Ashburn.*

Exercise Testing With Multiple Leads in Patients With and Without Previous Myocardial Infarction

JULIO F. TUBAU, MD

A MAJOR QUESTION in exercise testing has been how many electrocardiographic leads are needed for the optimal detection of coronary heart disease? Attempts at improving accuracy have been made using multiple leads,[20] different criteria for a positive test[21] and computer analysis of the electrocardiogram.[22,23] The importance of prevalence and the extent of coronary disease have been found to have a serious impact upon the predictive value and sensitivity of exercise ECG's.[24,25] Since prevalence of coronary heart disease is related to clinical presentation, evaluation of exercise ECG's should consider patients in different categories of symptoms and clinical presentations. For the purpose of this discussion, patients have been classified as those with typical angina, those with probable angina and those with symptoms of atypical or nonischemic chest pain. Existence of a previous myocardial infarction is obviously associated with a high prevalence of coronary heart disease.[26] Exercise testing is used in this group of patients to detect occlusive disease in other vessels than the one related to the myocardial infarction.

This section will review the usefulness of a comprehensive approach to exercise testing with multiple leads in two populations: first, 200 consecutively seen male patients without previous myocardial infarction with a normal resting electrocardiogram; second, 118 men surviving a transmural myocardial infarction.

Methods

Patients exercised on a treadmill following a modified Bruce protocol.[27] The electrocardiogram obtained consisted of 14 leads including the standard 11 but excluding AVR and bipolar leads CC_5, CM_5 and ML (ML was formed by electrodes placed on the manubrium and the flank). Criteria for a positive test were horizontal or down sloping ST segment depression more than 0.1 millivolt for 0.08 second or an ST segment slowly upsloping with depression more than 0.2 mV at 80 msec after the J-point.[21] All negative tests had to exceed at least 85 percent of the age-predicted maximal heart rate to be considered maximal. Coronary angiography was carried out the day after the exercise test. Selective coronary arteriography was done using a percutaneous technique.[28] A lesion greater than 70 percent of the arterial luminal diameter was considered significant except for the left main coronary artery where stenosis equal to or greater than 50 percent was considered significant. Left ventricular wall motion was assessed qualitatively by an experi-

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TABLE 1.—*Diagnostic Values of Exercise Testing in Different Clinical Subsets*

Clinical Subsets	Lead System			
	V_5	CM_5	CC_5-CM_5-ML	14L
Typical or probable angina (N=151)				
Sensitivity	0.61	0.74	0.83	0.85
Specificity	0.91	0.77	0.76	0.76
Likelihood ratio (+)	6.78	3.08	3.46	3.58
Likelihood ratio (−)	2.33	2.92	4.47	5.43
Atypical chest pain (N=49)				
Sensitivity	0.50	0.57	0.64	0.64
Specificity	0.86	0.74	0.69	0.69
Likelihood ratio (+)	3.57	2.19	2.07	2.07
Likelihood ratio (−)	1.72	1.72	1.92	1.92

enced radiologist and recorded as normal, hypokinetic, akinetic and dyskinetic.

Coronary Artery Disease Without Previous Myocardial Infarction

Symptoms

The 87 patients presenting with typical angina had an 86 percent prevalence of coronary heart disease, the 64 with probable angina had a prevalence of angiographic disease of 65 percent, and of 49 with nonspecific chest pain 28 percent had disease. The severity and distribution of coronary stenosis were similar in patients with typical or probable angina but much less severe in patients with atypical symptoms. Fewer patients in this latter subset had three-vessel disease or proximal left anterior descending stenosis (7 percent versus 32 percent and 7 percent versus 34 percent, respectively—$P=0.05$). Symptoms were clearly related to the severity of the lesions.

Multiple Versus Single Leads

Sensitivity increased using multilead systems in all subsets of patients with only a minor reduction in specificity. The efficiency of the test—that is, the percent of patients correctly classified—increased when multiple leads were used in patients with typical and probable angina but decreased in patients with atypical symptoms because of an increase in false-positive results. Three-vessel disease and left main disease were better detected in patients with typical and probable angina using the 14 leads. The combination of ST segment depression and total treadmill time was better able to separate patients with severe coronary artery stenosis, particularly in subsets other than those with atypical chest pain. For instance, a positive test with the 14 leads and a total treadmill time less than or equal to six minutes detected 58 percent of patients with three-vessel disease and 86 percent of patients with multivessel disease. Conversely, a negative exercise test going into Bruce stage III (greater than nine minutes) in patients with typical or probable angina was associated with only 15 percent having multivessel disease and 5 percent with three-vessel or proximal left coronary disease. Patients with nonspecific chest pain were less benefited by this combination.

Because sensitivity and specificity were different for the patients with typical and probable angina compared with those with nonspecific chest pain, the likelihood ratios (LR)—the numerical value of the probability that a given test result is a true one versus a false one—were also different for the two groups of patients (Table 1). The ratio of an abnormal test is calculated by the formula: likelihood ratio (+) = sensitivity divided by one minus specificity. The use of this value in calculating the posttest risk of disease is exemplified by the following formula: Posttest risk of disease = pretest risk (prevalence) × LR(+). Since LR+ was lower for each lead system in the patients with nonspecific chest pain compared with more symptomatic patients, the calculation of posttest probability of disease may be incorrect using a single value of likelihood ratio for all patients; that is, since sensitivity and specificity change in populations with different prevalences of disease, likelihood ratios change.

In conclusion, exercise testing with multiple leads in subsets without previous myocardial infarction has its major contribution in patients with typical or probable angina. The combination of ST segment depression and treadmill time was useful for separating patients with and without multivessel disease or high-risk lesions. It is clear that predictive statements of the posttest risk of disease must be used carefully since their accuracy will depend upon the similarity between the popu-

lations actually examined and the population from which sensitivity and specificity values were derived.

Multivessel Disease and Previous Transmural Myocardial Infarction

We carried out studies in 118 men who survived a transmural myocardial infarction. The acute infarction occurred within a year in 75 percent of the patients. The other patients had silent infarctions or had a longer interval between infarction and subsequent coronary angiography but were similar to the entire group in regard to symptoms, electrocardiogram and angiographic data. The severity of the angina was classified according to the Canadian Cardiovascular Classification[30] (asymptomatic = 0; the presence of angina was coded as 1, 2 or 3 as to its occurrence during mild, ordinary or strenuous exertion, respectively).

Inferior Versus Anterior Infarction

The prevalence of multivessel disease in patients with *inferior myocardial infarction* was 68 percent. Of patients with mild symptoms (group A), 50 percent had multivessel disease compared with 80 percent of those with more symptoms (group B). When there were abnormal findings on an exercise ECG using 14 leads, 80 percent of patients with mild symptoms (group A) and 96 percent of those with severe symptoms (group B) were found to have multivessel disease. With a test showing no abnormalities, only 20 percent of group A patients and 56 percent of group B patients ($P = 0.05$) had multivessel disease. The prevalence of high-risk lesions (three-vessel and proximal left coronary artery stenosis) was 13 percent in group A patients, and a combination of abnormal findings on an ECG test and final treadmill time selected 60 percent of patients with that condition. A test showing no abnormalities was associated with that severe disease in only 4 percent of the cases. Thus, an exercise test is more useful in patients with few or no symptoms after an inferior myocardial infarction.

Patients with a previous *anterior myocardial infarction* had a 58 percent prevalence of multivessel disease. The extent and prevalence of multivessel disease did not correlate with angina class. The sensitivity of a 14-lead ECG was less for patients with anterior infarctions (64 percent) compared with inferior myocardial infarction (76 percent). Similarly to the inferior infarct patients, the maximum diagnostic information occurred in those with mild coronary symptoms (group A). An abnormal result of an exercise ECG detected 86 percent of patients with multivessel disease and a negative response excluded this condition in 70 percent of the cases. When considering depth of ST segment depression and total treadmill time it was possible to obtain additional information. A normal test finding in the 14-lead study through Bruce stage III decreased the probability of three-vessel disease to 10 percent. A positive test with equal to or greater than 0.2 mV of ST segment depression and a final treadmill time less than six minutes increased the likelihood of three-vessel coronary disease to 64 percent. Survivors of an anterior myocardial infarction presenting with more severe symptoms benefited less from exercise testing.

TABLE 2.—*Detection of Multivessel Disease After Transmural Myocardial Infarction (MI)*

Infarction Location	*Lead System*		
	V_5	CC_5-CM_5-ML	*14L*
Inferior MI (N=75)			
Sensitivity	0.22	0.69	0.77
Specificity	0.96	0.88	0.79
Anterior MI (N=43)			
Sensitivity	0.4	0.56	0.64
Specificity	1.0	0.83	0.67

ST Segment Elevation

Isolated ST segment elevation was associated with the corresponding akinetic or dyskinetic wall motion abnormality in 92 percent of the cases. The inclusion of ST segment elevation in the criteria for positivity did not augment the sensitivity of the test.

Chest Pain

The presence of angina during exercise testing by itself was a powerful predictor of multivessel disease. Of 45 patients with this finding, 40 had multivessel disease. The absence of angina during the test did not exclude multivessel disease because 50 percent of the patients without angina had this disease.

Choice of Lead Systems

The utilization of multilead systems increased sensitivity with a slight decrease in specificity (see Table 2). Overall, these findings suggest that a combination of V_5 and two bipolar leads (CC_5 and CM_5), in addition to being simpler, provides similar predictive information with only an 8 per-

cent decrease in sensitivity compared with the 14 leads. This latter study was obtained in a selected population which excluded nontransmural myocardial infarction and may not be generally applicable for all those who have had a myocardial infarction.

Conclusions

These studies show that the modern approach to exercise testing takes into account symptoms before interpreting exercise ECG results. The electrocardiographic response must be weighed differently depending upon the pretest risk of disease.

Second, interpreting exercise test results must include other variables in addition to just abnormal ST segment depression. For example, the depth of ST segment depression and treadmill time provide valuable diagnostic information.

DR. FROELICHER: *The work from the Montreal Heart Institute has been very valuable in applying Bayesian statistics and the predictive model to clinical exercise testing. Dr. Tubau has excellently summarized this. V_5 or a similar left precordial lead is the most sensitive and may be all that is necessary in patients with a normal resting* ECG *and without a history compatible with coronary artery spasm or myocardial infarction. Anterior, lateral and inferior leads are essential in patients with abnormal* ECG*'s, an old myocardial infarct or a history compatible with spasm.*

Dr. Costello and Dr. Glover will now present a summary of the use of two-dimensional echocardiography in evaluating coronary heart disease.

Two-Dimensional Echocardiography

DENNIS COSTELLO, MD
MATTHEW GLOVER, MD

ULTRASONIC METHODS have been used to study the structure and function of the heart in health and disease since Edler and Hertz[31] in 1954 first recorded the motion of the mitral valve and posterior left ventricular wall by M-mode techniques. In the last decade M-mode echocardiography has provided accurate and relatively inexpensive diagnostic and serial follow-up information on patients with congenital, valvular, pericardial and myopathic heart disease.

The M-mode technique additionally has been widely employed as a means of determining the size and function of the left ventricle. Various investigators[32-35] have shown an excellent correlation between echocardiographic and angiographic left ventricular volume and ejection fraction. Such calculations of left ventricular size and function assume that the internal diameter of the left ventricle obtained by the single beam of the M-mode technique was representative of the contraction pattern of the left ventricle as a whole. In patients with coronary artery disease and previous myocardial infarction, asymmetry of contraction commonly is seen, and thus this single view obtained by the M-mode echo may not be representative of the entire left ventricular contraction pattern. Teichholz has clearly shown the limitations of such volume and ejection fraction determinations in patients with coronary artery disease and asymmetry of contraction.[36]

Such limitations of quantitative evaluations of left ventricular performance with one-dimensional ultrasonic techniques prompted increased interest in two-dimensional methods. Such methods would allow for special orientation of the heart with real-time viewing of the entire left ventricular silhouette including areas of left ventricular asynergy. The initial two-dimensional studies employed B-mode scanning techniques and were moderately successful,[37] although difficulties with tangential views, arrhythmias and chest and transducer motions tended to distort the cardiac silhouette.[38]

Equipment and Recording Techniques

The two commonly employed devices for obtaining two-dimensional images are the mechanical arc sector scanner[39] and the phase-array scanner.[40,41] The mechanical scanner uses a single beam which is swept mechanically through a given arc by a small motor. The phase-array scanner uses an electronic beam guided over an 80° arc.

Studies are carried out with patients in the supine or left lateral decubitus position. A complete two-dimensional examination includes long- and short-axis views obtained with the transducer in the parasternal position and apical two- and four-chamber apical views as previously described[42] (Figures 6 and 7). Suprasternal notch placement of the transducer may also be used for long-axis viewing.[43] Such views provide for

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adequate examination of the anterior, lateral, posterior, septal, inferior and apical segments of the left ventricle, as well as right ventricular and left and right atrial images.

Left Ventricular Function

M-mode echocardiography reliably predicts left ventricular function in patients with symmetrically contracting left ventricles. In patients with regional asynergy two-dimensional echocardiography may provide an accurate prediction of left ventricular ejection fraction.[42-46] Two-dimensional determinations of left ventricular volume have been shown to be less accurate than ejection fraction calculations and generally underestimate the angiographic volume.[42-46] This unreliability of volume determination may relate to tangential viewing and thus the underestimation of the true ventricular circumference.

Regional Asynergy

Two-dimensional techniques, particularly the apical views, are particularly useful in assessing regional wall motion abnormalities. Such real-time viewing of the anterior, lateral, posterior, inferior and apical segments can provide reliable

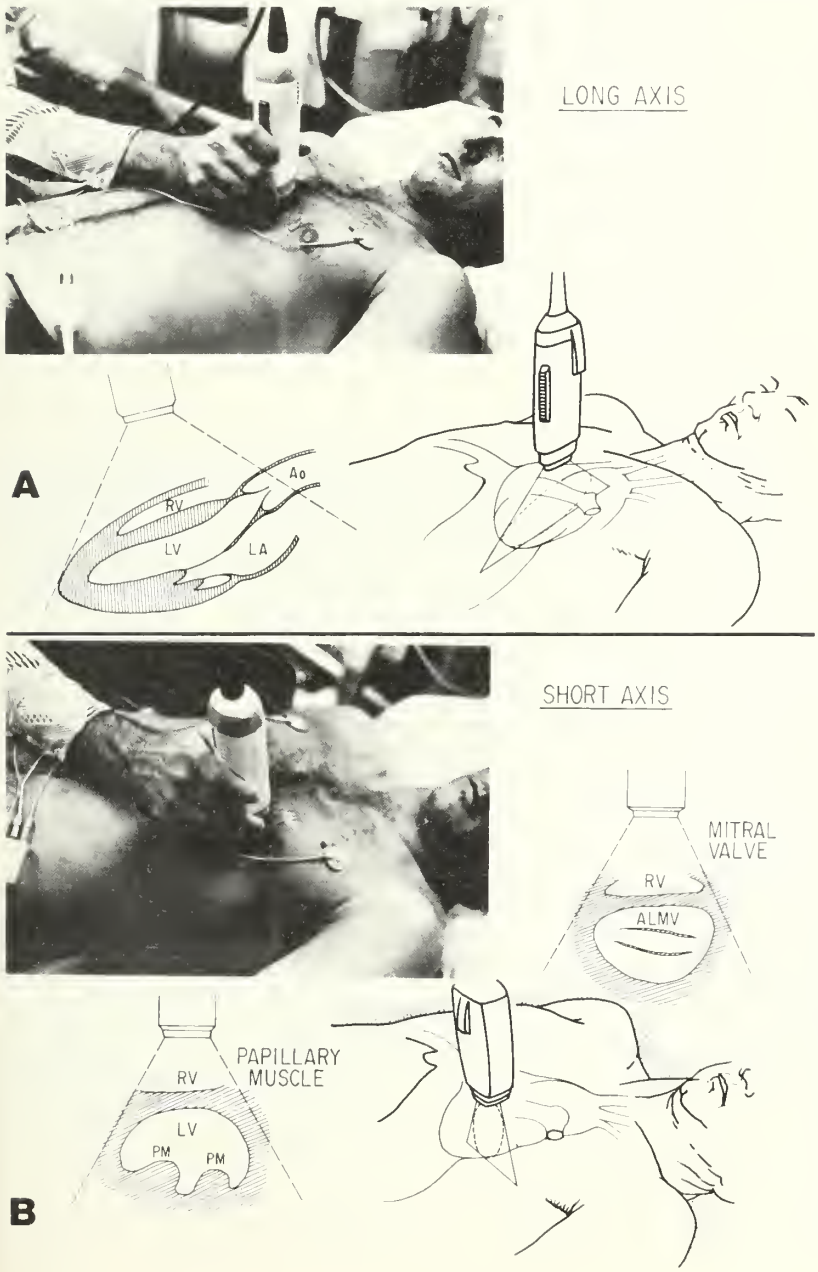

Figure 6.—Conventional precordial long axis **A**, and short axis **B**, two-dimensional views. The long axis view is useful for viewing the intraventricular septum, posterior left ventricular wall and anterior leaflets of the mitral valve. The short axis view may be obtained at the level of the mitral valve or at the level of the left ventricle in the region of the papillary muscle (PM). (Reproduced from Carr et al[42]; with permission of the American Heart Association, Inc., and the authors.)

information regarding wall motion disorders and ventricular aneurysms. Kisslo and co-workers[47] showed there to be a high correlation between angiographic and two-dimensional analyses of wall motion in 105 patients. Weyman and associates[48] were able to detect or localize ventricular aneurysms in 31 patients, including 16 in whom visualization by M-mode techniques previously had not been done (Figure 8).

Left ventricular pseudoaneurysms may additionally be identified with two-dimensional echocardiography.[49] Catherwood and co-workers[50] have recently suggested that pseudoaneurysms may be distinguished from true aneurysm by the narrow

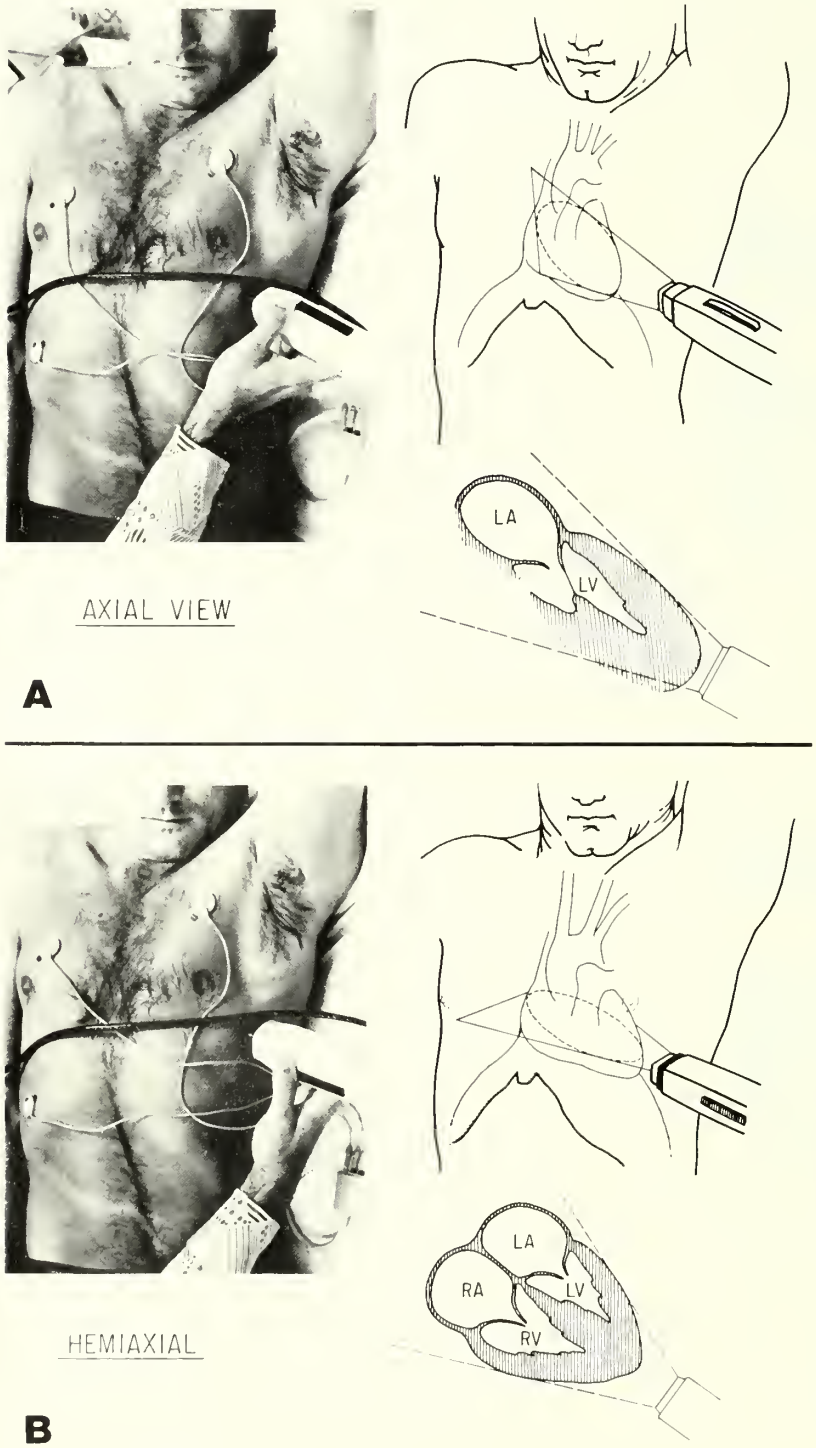

Figure 7.—The apical two-chamber (axial) **A** and four-chamber (hemiaxial) **B**. Views are obtained with the transducer located at the apex and directed toward the right shoulder. The two-chamber view transects the true anterior and posterior walls of the left ventricle and the left atrium. The four-chamber view images all four cardiac chambers as well as the interventricular septum and posterior lateral wall. (Reproduced from Carr et al[42]; with permission of the American Heart Association, Inc., and the authors.)

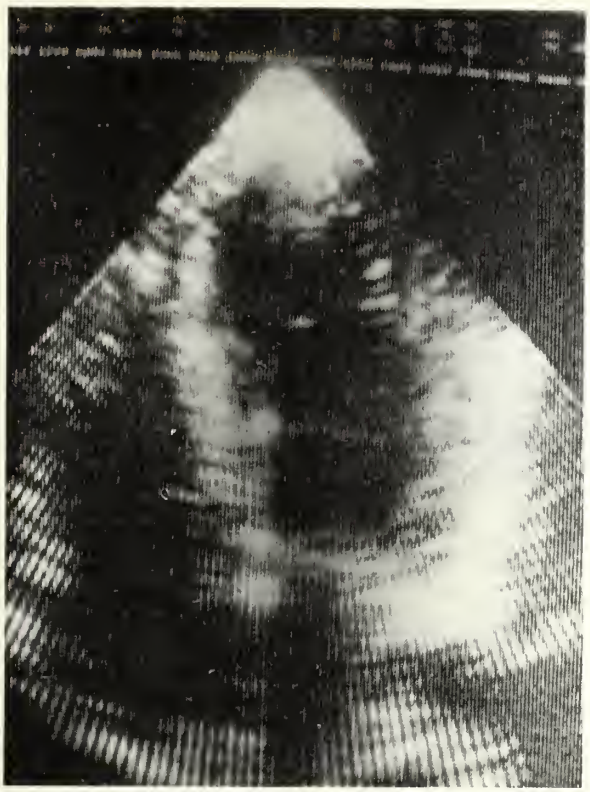

Figure 8.—Apical four-chamber view showing systolic apical dyskinesis and apical left ventricular thrombus.

ostium, sharp discontinuity of endocardial image and saccular appearance of the pseudoaneurysm chamber (Figure 9).

Acute Myocardial Infarction

Two-dimensional echocardiographic studies may be carried out in cases of acute infarction. Eaton and associates[51] have attempted to relate serial changes of left ventricular function following infarction with overall survival. In 8 of 28 patients, left ventricular dilatation was shown on serial studies done during the first two weeks following infarction. Only four of the eight patients with dilatation survived longer than two months. Thus, two-dimensional echocardiography may be employed to follow serial changes in left ventricular function in the acute phases of infarction.

Two-dimensional echocardiograms may also be useful in identifying mechanical complications of acute infarction. Postinfarction ventricular septal defect[52] (Figure 10), head of a papillary muscle rupture and pseudoaneurysm[49,50] formation have been identified. Such instances may be suspected when a patient's clinical status has deteriorated out of proportion to the extent of left ventricular dysfunction.

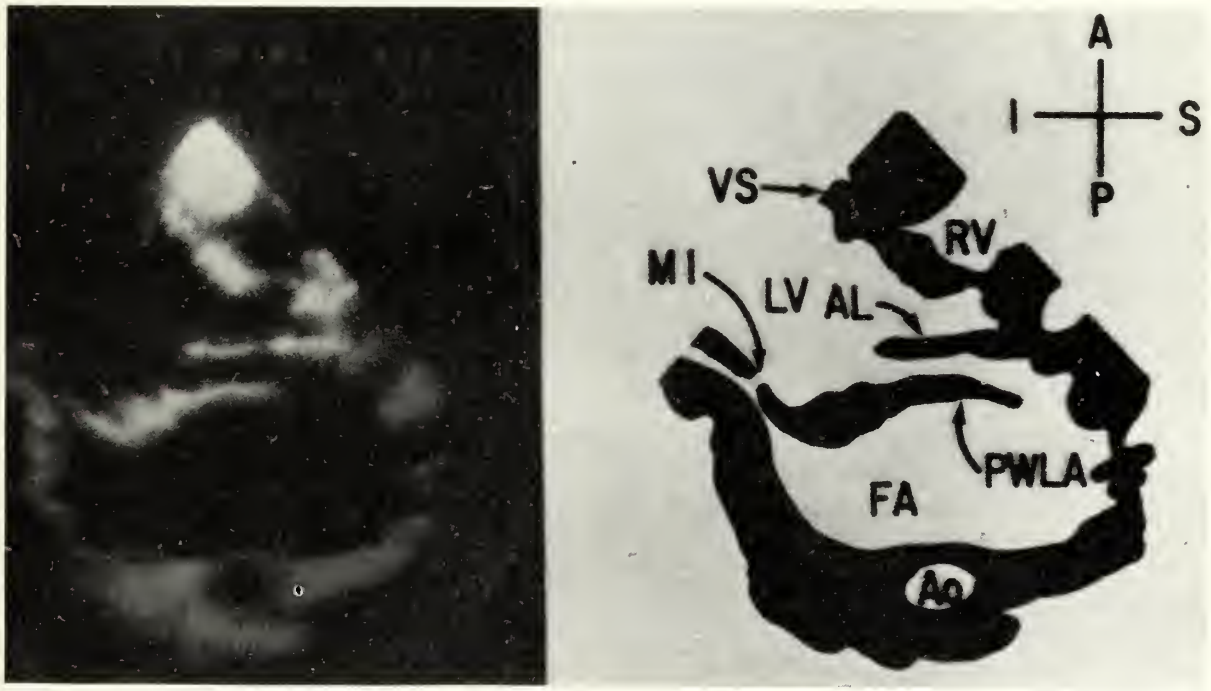

Figure 9.—Two-dimensional echocardiographic demonstrations of a false aneurysm (FA) of the left ventricle (LV). The aneurysm originates from a region of myocardial infarction (MI) with a thinned segment of the posterior wall. The aneurysm is located posterior to the left atrium (PWLA). The anterior leaflet of the mitral valve (AL), ventricular septum (VS) and right ventricle (RV) are illustrated. (Reproduced with permission of Military Medicine and the authors Glover M, Hagan A, Ceretto W, et al: Pseudoaneurysm of the LV diagnosed by two-dimensional echocardiograph, in press.)

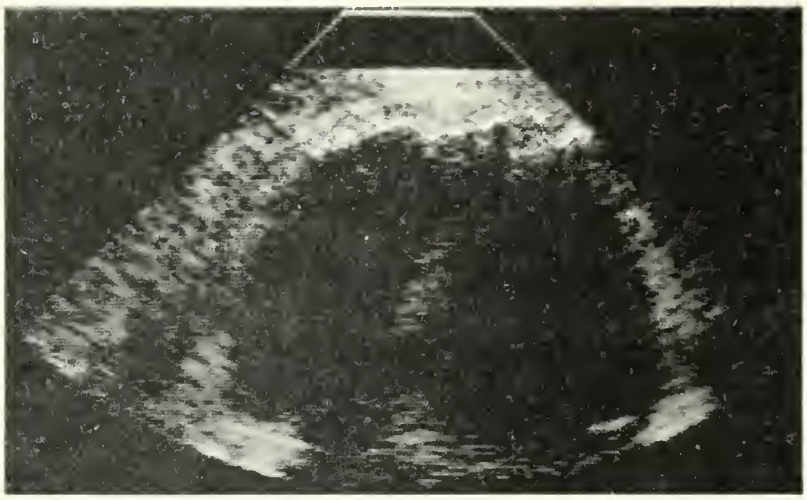

Figure 10.—Apical four-chamber view showing systolic proximal interventricular septal thinning and aneurysmal bowing toward the right ventricle with echo dropout consistent with a postinfarction ventricular septal defect. Right heart enlargement is also present.

Left Main Coronary Artery

Several investigators[53,54] have demonstrated the capability to echo the region of the left main and proximal left anterior descending coronary artery. A stenosis may be identified as a disruption or narrowing of the echo-free space of the coronary lumen. Although still in the experimental phase, two-dimensional echocardiography may prove to be useful in the identification of high-risk patients with significant left main coronary obstruction.

Summary

In summary, two-dimensional echocardiography is rapidly becoming an effective, relatively inexpensive and safe method of noninvasively evaluating and serially following up patients with coronary artery disease, as well as many other varieties of cardiac disease.

DR. FROELICHER: *We very much appreciate the illustrations (Figures 6 through 10) provided by Dr. Matthew Glover, from the Naval Regional Medical Center in San Diego, that accompany Dr. Costello's presentation. Two-dimensional echocardiography is becoming an essential tool in the evaluation of cardiac diseases and its uses in coronary heart disease are well summarized here.*

The final presentation will be by Dr. Tubau. Dr. Tubau has been working with us for one year in Dr. Ashburn's nuclear medicine laboratory. He has continued the work of Dr. Robert Slutsky, who is finishing his Clinical Cardiology Fellowship Training at the University of California, San Diego. Previous work has shown that ejection fraction can be accurately and reproducibly measured using radionuclide techniques at rest and during exercise, and Dr. Slutsky has presented data that volume changes can be measured. Dr. Tubau here presents a summary of the different methods of determining left ventricular volume using radionuclide techniques.

Left Ventricular Volume Determined by Radionuclide Techniques: A Review

JULIO F. TUBAU, MD

THE DETERMINATION of left ventricular volume provides a better understanding of the pathophysiology of heart disease than does ejection fraction alone. In clinical practice, left ventricular volume is of proven value as a prognostic index in patients with valvular regurgitant lesions. The ability to assess left ventricular volume changes in response to exercise, drug administration or other interventions is exciting because it has impact on wall tension, one of the major factors influencing myocardial oxygen demand. The following two different noninvasive radionuclide approaches to measuring left ventricular volume at rest and during stress are possible: one, using first-pass imaging and, two, using equilibrium radionuclide angiography.

First-Pass Methods

The study of heart function using the first transient of a radionuclide bolus through the central

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circulation has been well-studied.[55] In brief, radioactivity in the left or right ventricle during the first circulation of a radionuclide tracer is proportional to the amount of blood in the chamber at any time. By sampling the radioactivity over time in the left ventricle using a standard gamma camera and a dedicated computer, it is possible to obtain a time-activity curve for each heart beat during several cardiac cycles. The time-activity curve is equal to the amount of radioactivity or counts over time and usually three to eight heart beats are included. After subtraction of the background activity, a time-activity curve with a high sampling rate (25 points per second) is obtained. It consists of a succession of peaks and valleys where the peaks correspond to end-diastole and the valleys to end-systole. Ejection fraction (EF) is obtained by averaging several heart beats using the following formula (with EDV indicating end-diastolic volume and ESV indicating end-systolic volume):

$$EF = \frac{\text{EDV counts} - \text{ESV counts}}{\text{EDV counts}} \times 100$$

Ejection fractions obtained with this method correlate well with contrast biplane ventriculography (r approximately 0.9). Images obtained at 25 to 50 msec intervals from several cardiac cycles of similar duration and characteristics are superimposed in order to obtain high fidelity images that can be displayed in movie format for qualitative analysis of wall motion. Left ventricular volumes can then be obtained by planimetry of the end-diastolic frame images using a similar technique to that described by Dodge and associates[56] for contrast ventriculography. This method postulates that the left ventricular cavity can be represented by an ellipsoid.

$V = 4/3\ \pi \frac{Da}{2} \times \frac{D1}{2} \times \frac{L}{2}$, assuming that both minor axes are equal—that is, $Da = D1$. $V = \pi\ 16 \times D^2L\ (CF)^3$ where CF is a correction factor for x-ray image distortion. The same methodology seems applicable to the radionuclide angiogram in the anteroposterior or right anterior oblique projection.

Rezych and co-workers using this method derived cardiac output from the ejection fraction (EF), left ventricular end-diastolic volume (LVEDV) and heart rate (HR) (cardiac output = EF × LVEDV × HR).[56,57] The correlation coefficient between simultaneous ICG (indocyanine green) dye cardiac output and calculated radionuclide cardiac output was 0.95. It should be noted that resting and exercise values for the same patient were included in the correlation coefficient analysis.

A second possible way to calculate ventricular volume is to derive its value from the cardiac output calculated directly from the first pass of the radionuclide through the central circulation.[58] A calculation of cardiac output noninvasively using this method is very simple based on the indicator dilution principle. In short, a curve similar to the one obtained using ICG dye and a cuvette densitometer is provided by using a gamma camera to sample a radionuclide substance passing through the heart. The integration of the area under the curve is proportional to cardiac output. The values obtained with this method correlate well with those of the ICG technique ($r = 0.95$). It is possible using the cardiac output and EV values to derive left ventricular volume using the formula LVEDV = cardiac output/EF × HR.

Equilibrium Multiple-Gated Blood Pool Imaging

This technique is based on the administration of a radioactive substance that remains relatively stable in the circulation for a period of four to six hours. The most common substance employed in clinical studies is technetium 99m linked to human serum albumin or red blood cells. Stannous salt helps technetium bind to red blood cells and is usually added.

Using a standard gamma camera and a dedicated computer, the radioactivity in the left ventricle is assessed through the entire cardiac cycle. Because the amount of radioactivity in one cycle is insufficient for imaging, the study requires the accumulation of counts through 300 or more heart beats.

Once the radioactive substance has reached equilibrium in the blood pool, the study is carried out in the following way. Using the R wave of the electrocardiogram as a reference point, the R-R interval is divided into several equal portions (12 or more have been used) and the information of each corresponding portion of each cycle added forming the same number of composite images based on all 300 cycles. The movie format display of the images is used for the assessment of wall motion and the count rate changes through the cycle are used for constructing a time-activity curve. Ejection fraction is then obtained by the formula: EF = end-diastolic counts minus end-systolic counts (all background-cor-

rected values) divided by end-diastolic counts. End-diastole and end-systole are considered the higher and lower values of the curve. A point-by-point comparison of the left ventricular volume curve obtained by contrast ventriculography and the time-activity curve with radionuclides has a good correlation value ($r=0.93$).[59] If it were possible to convert counts to millimeters, the volume calculated by this method would be of great value because, in addition to being noninvasive, it is less influenced by the inherent errors of *geometrical assumptions*. The following will be a review of several methods already being used for research purposes using this technique.

General Theoretical Assumptions

If the distribution of the radioactive tracer in the blood is homogeneous, the radioactivity per milliliter of a sample of peripheral blood may be used to calculate the counts in the left ventricle at any time during the cardiac cycle with the actual volume. Left ventricular volume equals total counts in the left ventricle (at a particular time of the heart cycle) divided by activity per milliliter of the blood sample. In order to make an appropriate conversion several factors are important: (1) the time during which the reference blood sample and the left ventricle counts are obtained is normalized, (2) the radioactive decay is considered when there is a significant difference in time from the sampling of peripheral blood and when the radioactivity assay of the sample is done and (3) attenuation factors must be considered.

The first two factors are relatively easy to account for in calculating volume. In brief, the radioactivity or number of counts at end-diastole are theoretically the same for all cycles processed so if the time per frame (R-R interval in seconds divided by number of frames) and the number of heart beats processed is known, the counts at end-diastole per single beat per unit of time can be easily calculated. The second factor involves a very simple calculation; the counts at a given time (Ct) are equal to counts at time zero when the sample was obtained times e^{-dt} (formula: $Ct = Co \times e^{-dt}$) where d is the decay constant assuming a half-life of six hours and t the time between the blood sampling and counting.

The most controversial factor is attenuation. In an intuitive way, it is obvious the reference blood sample should be counted at a similar distance from the camera as the left ventricle. In addition, there is lung and soft tissue between the heart and the camera that may equally influence the amount of radioactivity arriving at the camera. The main factors influencing the amount of radioactivity seen by the camera include (1) the distance and (2) the kind of tissue interposed between the heart and the camera. If we assume a source at a distance (d) separated from the camera by a tissue of attenuation characteristics defined by a coefficient r, the counts arriving at the camera (Cc) will be equal to the real counts (Cr) times e^{-rd}. When considering a dimensioned source like the left ventricle, it is obvious that the distance will be shorter for the anterior portion of the ventricle compared with the most posterior portion. The radioactivity from this posterior region of left ventricle will have to cross the whole thickness of blood inside the left ventricle in addition to the soft tissue, so the left ventricular geometry may play a significant role in the calculation of ventricular volumes. The complexity of the issue has resulted in two approaches to the problem: one that does not account for attenuation and a second that does.

TABLE 3.—*Equilibrium Radionuclide Angiography-Volume Correlation*

Center	N	r Value		SEE (ml)	
		EDV	ESV	EDV	ESV
UCSD	17	0.97	0.98	12	7
Dallas	22	0.98	0.98	16	15
Boston	13	0.86	0.91	36	22
J. Hopkins ..	22	0.94	0.95	..	..
J. Hopkins ..	22*	0.96	0.96	33	33

EDV = end-diastolic volume; SEE = standard error of the estimate; ESV = end-systolic volume

*Accounting for attenuation.

Methods That Do Not Involve Attenuation Factors

These methods (UCSD,[60] Dallas,[61] Boston[62]—Table 3) are very similar to one another and they consider all other factors except attenuation. In brief, the background-corrected counts in the left ventricle are obtained from the time-activity curve using a semiautomated computer program or by manually assigning a region of interest around the left ventricle at end-diastole and end-systole. A blood sample (3 to 5 ml) is drawn in the middle of the study and counted in front of the camera. The background-corrected counts per milliliter are used to calculate volume units from counts in the left ventricle. LV unit = LV counts divided by

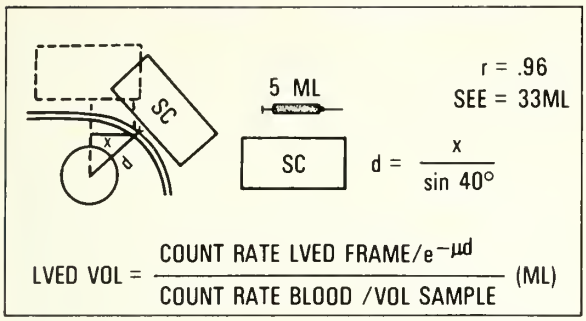

Figure 11.—The measurement of the projection of d on the frontal plane X is measured easily over the computer's television screen in pixels and converted to cm by a conversion factor.

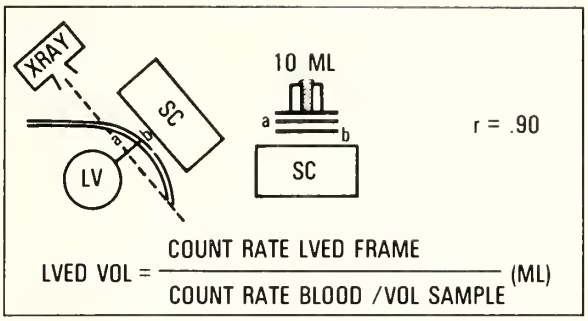

Figure 12.—The distance from the skin to the left ventricle is assessed by an orthogonal 6-foot x-ray film. The source is imaged through air (b) and "soft tissue" of thickness a.

counts per milliliter of blood sample. These three reported methods were found to have a very good correlation between the radioactive volume units and the left ventricular volumes calculated from contrast ventriculography with both procedures performed within 24 to 48 hours ($r=0.86$ to 0.98, see Table 3). The equation obtained from the regression line can be used to convert volume units into milliliters. Using this methodology all studies were able to calculate real volumes; the difference between radionuclide and angiographic volumes was significant as assessed by the standard error of the estimate values (SEE).

Methods Correcting for Attenuation

Two methods have been proposed that consider attenuation. The theoretical advantage is to avoid the utilization of a regression equation that has the potential error of disparities between the population of reference used to calculate the equation and subsequent patients. One of the methods uses an attenuation factor obtained by calculating the distance between the camera and the theoretical center of the left ventricle based on the linear attenuation coefficient of water.[63] The volume is then calculated from the formula:

$$\text{LVEDV} = \frac{\text{count rate from LV in end-diastole } / e^{-\mu d}}{\text{count rate per milliliter of blood sample}}$$

The calculation of the distance (d) is relatively simple (Figure 11). A radioactive point source is positioned over the left ventricle in the 40° left anterior oblique (LAO) projection and fixed on the chest. The left ventricle and the source are imaged in the posterior-anterior view. The calculation of d is obvious: $d=x$ divided by sine 40°. Using this method a very good correlation was obtained with contrast angiography ($r=0.96$). The standard error of the estimate was not different from the one obtained by other investigators without considering attenuation. In fact, in this particular study, the correlation was similar whether considering attenuation factors or not. When estimating the distance from the camera to the left ventricle, a difference of 1 cm represented a 14 percent change in the calculated left ventricular volume. The authors claimed that the calculation of this parameter was very reproducible. No correlation was found between the distance (d) and the calculated volume or the body surface area or body habitus that could obviate its calculation.

Other groups of investigators have proposed correcting for attenuation by calculating the thickness of soft tissue between the left ventricle and the skin, using an x-ray along the camera axis (Figure 12).[64] The correction factor would be incorporated when imaging the blood sample at the same distance that the camera was from the chest and with the interposition of the same thickness of material with an attenuation similar to soft tissue.

Discussion

Left ventricular measurements are very important for the assessment of left ventricular performance. The use of percentage changes has already been very reliable and helpful, but in certain circumstances it is important to obtain an accurate absolute value, particularly for its prognostic implications.[64,65] First-pass methods using area-length analysis are more problematic than equilibrium methods because of the difficulty in being reproducible with planimetry of a small image. In addition, this method encounters more problems when used to assess several interventions in the same patient since it requires several injections of radionuclide tracer. Equilibrium methods

have problems as well. In general, it seems that radionuclide left ventricular measurements underestimate angiographic volumes when the region of interest around the left ventricle is defined semiautomatically with a computer-derived algorithm rather than defined manually. Although the methods described here seem to be very promising, they are in general time consuming and their reproducibility, interobserver variability and accuracy in larger patient populations need to be assessed before they become routine clinical tools.

DR. FROELICHER: *In concluding this specialty conference, it is necessary to emphasize that some of the techniques described are still in the investigative stage, while others are clinically applicable. Within the latter category are included the electrocardiogram, the exercise test and two-dimensional echocardiography. However, the potential for further improvements in the usefulness of all of these techniques can only be reached by further research. Though previously recommended noninvasive techniques have always been replaced by even* better *ones and the earlier ones then said to be inaccurate, it is still not unreasonable to hope that in the future it will be possible to reliably assess a patient with coronary heart disease by applying a combination of indirect methods. This would obviate the need for cardiac catheterization and angiography in many patients. The imaging techniques (two-dimensional echocardiography and radionuclide ventriculography) offer an exciting improvement over previous noninvasive techniques because they enable direct visualization of the heart. Recently, much excitement has been generated by digital image processing of both intravenous injections of contrast media and two dimensional echocardiograms. Perhaps our next symposium on noninvasive techniques will conclude that cardiac catheterization is obsolete except as a roadmap for coronary artery bypass operations, but that is not the case now.*

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Refer to: Becker CE: Acute methanol poisoning—'The blind drunk'—Medical Staff Conference, University of California, San Francisco. West J Med 135:122-128, Aug 1981

Acute Methanol Poisoning

'The Blind Drunk'

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Grand Rounds, Dr. Charles Becker will present an unusual case of methanol poisoning and discuss its pathophysiology and management.*

Case Presentation

DR. BECKER:† The patient, a pathology resident, was in excellent health until two o'clock one afternoon. While doing an autopsy she noted a peculiar whiteness to her vision, "like stepping out into a snow field." There was no associated diplopia or blurred vision. The only associated symptom was mild restlessness and shortness of breath, even with minimal exertion. She had taken two aspirin tablets in the morning for a mild headache. These symptoms continued and became severe over the next four to five hours when she sought assistance in the emergency room. She had not eaten or drunk anything unusual in the preceding 24 hours. The previous evening she had eaten a home-cooked meal. With that evening meal, approximately 12 hours before the onset of symptoms, she had consumed 30 to 60 ml of 86-proof vodka that was kept in the refrigerator and had been used on several earlier occasions; she also drank two glasses of wine. Her past medical history was normal except for mild labile hypertension and pyelonephritis.

In the emergency room she appeared healthy. She was afebrile, blood pressure was 170/105 mm of mercury, pulse 110 per minute and regular, and respirations 30 per minute. Findings on physical examination were entirely normal, including results of a detailed eye examination.

Routine laboratory studies gave the following values: serum sodium 135 mEq, potassium 4.7 mEq, chloride 107 mEq and bicarbonate 6 mEq per liter. Serum osmolality was 325 mOsm per kg of water, pH 7.21, carbon dioxide pressure (P_{CO_2}) 11 mm of mercury and oxygen pressure (P_{O_2}) 123 mm of mercury. Blood urea nitrogen (BUN) was 12 mg and creatinine 1.0 mg per dl. Leukocyte count was 7,000 per cu mm. Hemoglobin and hematocrit were within normal limits. Analysis of urine showed a pH of 5.5 with no crystals evident. Electrocardiogram showed only a sinus tachycardia. An x-ray film of the chest was normal. Blood methanol level was 140 mg per dl at 7 PM and 110 mg per dl at 9 PM. A blood salicylate level was undetectable.

Oral and intravenous administration of ethanol was begun and the patient was given sodium bicarbonate each hour. Hemodialysis was started and continued for six hours. At the end of dialysis

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no methanol was detected in her blood. The patient's visual symptoms decreased dramatically during dialysis. Extensive ophthalmological investigations indicated only slight pallor of the optic disc. Evoked visual responses eight hours following dialysis were normal. The patient fortunately has had an uneventful recovery. Police investigators on the night of admission secured the vodka bottle from her refrigerator; analysis showed a 20 percent methanol content.

Methanol Toxicology

Methanol (methyl alcohol or wood alcohol) is obtained from the destructive distillation of wood. This distillation is accompanied by a distasteful smell that limits the palatability of methanol. With further distillation, the pure methanol is much more palatable and has many industrial and practical uses. Methanol is found in varnishes, shellacs, duplicating fluids, stains, enamels, plastics, films, textiles, linoleum, dyes, explosives, rubber and felt hats. Because methanol can be derived from a large number of unused or discarded sources and has excellent combustion and mixing properties, it has been proposed as a gasoline additive, as home-heating material and as a feedstock for bacterial synthesis of feed protein. Most of us recognize methanol in the form of canned heat, such as Sterno, or in windshield-washing material.

Crude wood alcohol contains many impurities, which give it a disagreeable odor and taste. When the odor is removed, methanol becomes palatable and yields an increase in accidental and deliberate poisoning, which can reach epidemic proportions.

The toxicology of methanol was not initially appreciated. Some wines, brandies and whiskeys were sold in New York City during the late 1800's that contained substantial percentages of methanol. Initially, apparent poisonings were attributed to contaminants such as acetaldehydes, allyl alcohols, acetone or fusel oils. Results of early experiments with animals were inconsistent in describing methanol's toxicity. It was not until the 1920's, when a group of dock workers in Hamburg, Germany, were poisoned with chemically pure methanol, that the toxicity of wood alcohol was generally accepted. In the classic paper in the field Bennett and associates[1] reported their observations of 323 patients who had ingested bootleg whiskey in Atlanta during five days in October 1951. Forty-one deaths occurred when 90 gallons of illicit whiskey were distributed throughout the city. Later analysis of the confiscated material showed 35 percent to 40 percent methanol and less than 4 percent ethanol. As word of the poisoning spread, by rumor, newspaper and radio, a minor panic developed and numerous asymptomatic persons presented themselves to be checked for evidence of poisoning. In many instances these persons had drunk no alcoholic beverage at all and were simply frightened.

Kane and co-workers[2] reported an epidemic of poisoning in 18 persons, of whom eight died, when a diluted paint thinner was used as a source of alcoholic beverage in Lexington, Kentucky. The liquor was served as the major refreshment at a party. Naraqi and associates[3] reported a severe outbreak of methanol poisoning in Port Moresby, New Guinea, in March 1977 when 28 men attended a drinking party in which they consumed the contents of a drum that was found near their village. Some persons may have consumed as much as 600 ml of pure methanol in this epidemic. Four died, six had bilateral visual impairment and two had persistent difficulty with speech.[3]

Children have also been affected by methanol. A 10-week-old infant was admitted to hospital after methanol was mistaken for distilled water and mixed with her formula.[4] An 8-month-old child died in Brussels when methanol-soaked pads were placed on the child's chest to treat a common cold. This custom, known to the family as "take off the cold," was done by applying warm alcohol-soaked compresses to the child's chest, which had been previously rubbed with olive oil. Having no alcohol, the mother had accidentally purchased methanol-soaked pads.[5] The Polish literature[6] also contains the history of a painter who accidentally poured methanol on his clothes and shoes and did not change them; blindness developed within several days.

Pure methanol is a colorless liquid, having a specific gravity of 0.81, a boiling point of 65°C and a slight odor distinctly different from that of ethyl alcohol. Methanol can be absorbed through the skin, respiratory tract or gastrointestinal tract. Permissible exposure limits in industry, based on an eight-hour time-weighted average, have been estimated to be in the range of 200 ppm.

There is great variability in mean lethal dose among animal species. The special susceptibility of man to methanol toxicity is probably due to a metabolite of methanol (formate) and not to methanol itself. Reviewing clinical findings in epidemic situations or in isolated cases shows an enormous variation in the dose of methanol re-

quired to produce acidosis, blindness or death. Some of this clinical confusion may be explained by individual metabolic differences, associated ethanol consumption or availability of essential cofactors needed for methanol or formate metabolism. The smallest amount of methanol reported to cause death is 15 ml of 40 percent methanol; the highest dose recorded for a survivor is in the range of 500 to 600 ml.[3] Most cases of severe human poisoning occur by the oral route; occasional cases occur with skin contact and inhalation. Since methanol has a low boiling point and is completely absorbed from the mucous membranes of the upper respiratory passage, there is concern about methanol being applied to the inside of a windshield of a car in cold weather or about having repeated occupational exposures.

Methanol is rapidly absorbed from the gastrointestinal tract with peak absorption in 30 to 60 minutes. It distributes itself in total body water, although passage through all cellular membranes may be different from that of water, suggesting that some cells are less permeable. Bennett and co-workers[1] noted a higher concentration of methanol in cerebrospinal fluid than in blood in patients while the blood concentrations were declining. There is little evidence to suggest that methanol is actively concentrated in the central nervous system or in the cerebrospinal fluid.[7]

The primary route of elimination of methanol in humans is by oxidation to formaldehyde, formic acid and carbon dioxide. Methanol may also exit the body by induced vomiting, and a small amount is excreted in breath, sweat and urine. Increasing urine flow would be expected to increase methanol excretion to some extent, but forced diuresis would not be expected to significantly increase clearance of methanol.[7]

Several reviews[8,9] have described the metabolism of methanol and its metabolites in man. The difficulty in studying methanol toxicity in animals is that in nonprimates, doses of methanol that cause toxic reactions in man produce only intoxication similar to that seen with ethanol. Recent studies[10] using rhesus and pigtail monkeys have been able to provide a model for human methanol intoxication. In monkeys treated with formate alone, toxic effects develop in the optic nerve similar to those observed in humans.[11] Formate probably inhibits cytochrome oxidase in the fundi, disrupting the flow of the axoplasm and thus causing the pathological conditions in eyes.[11] Current evidence does not suggest that it is formaldehyde that causes these effects in the eyes. Rats do not accumulate formic acid because of their high rate of metabolism of formate; hence rats do not have the manifestations of methyl alcohol toxicity found in monkeys and humans.[11] A folate-dependent system is responsible for the oxidation of formic acid to carbon dioxide in the liver of monkeys and probably in humans. The level of folate appears to be critical for formate metabolism in animals. The classic symptoms of methanol toxicity in rats can be produced by rendering these animals folate deficient.[12] Experiments in monkeys strongly suggest that folate decreases formate accumulation after methanol overdose by stimulating formate oxidation, thus suggesting that folate may be useful in removing methanol.[13]

The enzyme primarily responsible for methanol oxidation is liver alcohol dehydrogenase (ADH). This enzyme has pronounced species variability. Ethanol has a higher enzyme affinity for alcohol dehydrogenase and is preferentially metabolized, whereas methanol is eliminated by nonmetabolic routes when ethanol is present. Ethanol concentrations of 100 to 200 mg per dl are clinically regarded as being optimal for saturating alcohol dehydrogenase to prevent methanol metabolism.[14] Although zero-order kinetics have been utilized to describe ethanol elimination, several investigators have shown a dose-dependent characteristic of ethanol.[14] Pyrazoles are known to be potent inhibitors of alcohol dehydrogenase. Pyrazole compounds in general are toxic to humans, but one particular pyrazole, 4-methylpyrazole (4MP), alone or in combination with ethanol may be of therapeutic value in methanol or ethylene glycol poisoning.[8,14-16]

Recent studies in isolated cases of methanol poisoning suggest that the associated metabolic acidosis is a result of formic acid accumulation.[17] The key role of formate causing the pathological damage to the eye and the acidosis has only recently been appreciated due to new techniques for the assay of formic acid. Thus, some of the variability in the toxicology of methanol is based upon susceptibility to folate deficiency, simultaneous alcohol consumption and total dose of the toxin ingested. Formaldehyde is highly reactive and its intracellular distribution in tissues has made it difficult to assess the role of this toxin in the pathology of methanol poisoning, but current evidence does not suggest that this is the primary pathological metabolite of methanol.

Pathological findings of methanol poisoning

have been described in detail.[1,8] The primary site of the ocular injury produced by methanol is in the optic nerve head and the intraorbital portion of the optic nerve rather than the retinal ganglia. Hemorrhage into critical portions of the brain is an important aspect of methanol poisoning. Cerebral computed tomography in methanol intoxication has shown necrotic areas of the putamen.[18] Pathological damage to liver, pancreas and kidney has also been described but is nonspecific.

Clinical Symptoms and Laboratory Findings

The time it takes for symptoms to develop and the identification of abnormal laboratory test results specifically referable to methanol poisoning depend on the amount of simultaneous ethanol ingestion and associated medical conditions. In epidemic circumstances the diagnosis may be easily recognized. However, in isolated cases, such as in our patient, the diagnosis may be confusing. Some idea as to the confusion that may arise in the clinical recognition of this disorder is illustrated by the following list of initial emergency room diagnoses in patients subsequently proved to have methanol poisoning: cholera, botulism, diabetic ketoacidosis, hangover, pancreatitis, renal stone, perforated peptic ulcer, intestinal obstruction, meningitis, brain tumor and subarachnoid hemorrhage.[1] Methanol may be ingested by alcoholic patients as an alcohol substitute. The sporadic case in a chronic alcoholic presents special problems for clinical diagnosis. It may be difficult to elicit symptoms of visual disturbances, and there may be a long delay in the onset of symptoms after ingestion. Associated head trauma may provide confusing neurological findings and early evidence of acidosis may be misinterpreted as alcoholic ketoacidosis.

The most important initial symptom, as graphically described by our patient, is indistinct vision frequently described as "like being in a snow storm." Visual disturbances are a universal complaint in the epidemic circumstance.[1] Complaints of blurred vision with a relatively clear sensorium should strongly suggest the diagnosis. Headache, dizziness, nausea, vomiting and abdominal pain may also be part of the associated symptoms with visual disturbances. Not infrequently, just as with our patient, there is a complaint of breathlessness, but Kussmaul-type respiration is not a prominent feature, even with pronounced acidosis. In severe cases, some persons have noted an odor of formalin on the breath or in urine. The development of bradycardia, prolonged coma, seizures and resistant acidosis indicate a poor prognosis.

$$Na + \frac{BS}{} + \frac{BUN}{26} = 285 \pm 4.2 \text{ mOsm/kg } H_2O$$

Figure 1.—Formula to calculate serum osmolality. (Na = serum sodium concentration mEq/liter/dl; BS = blood glucose concentration mg/dl; BUN = blood urea nitrogen concentration mg/dl.)

TABLE 1.—*Several Toxic Substances and Their Effect on Serum Osmolality at Their Lethal Blood Levels*

	Molecular Weight	*Estimated Lethal Levels (mg per dl)*	*Expected Osmalities (mOsm kg of water)*
Ethanol	46	350	80
Isopropanol	60	350	60
Ethylene glycol	62	200	40
Methanol	32	80	30
Ethchlorvynol	144	15	1

Physical findings are generally nonspecific. Fixed, dilated pupils have been described in severe cases. Results of ophthalmologic examinations may be normal, as in this case, but also may show severe hyperemia of the optic disc or retinal edema. Optic atrophy will be a late finding. On occasion, nuchal rigidity and signs suggesting meningitis may occur. Two thirds of patients may complain of headache associated with dizziness. The mode of death for most patients with methanol poisoning is a peculiar sudden cessation of respiration.[1,7]

Laboratory evidence of metabolic acidosis with an elevated anion gap and an osmolar gap strongly suggest the clinical diagnosis of methanol poisoning. A decreased serum bicarbonate concentration is a uniform feature of severe methanol poisoning. Just as in our patient today, there is a pronounced anion gap which is not explained on the basis of diabetic acidosis, lactic acidosis, uremic acidosis, starvation or alcoholic ketoacidosis. Ethylene glycol, paraldehyde and salicylate are also specific toxins that may cause an anion gap. Ethylene glycol will usually not cause visual symptoms and may be associated with oxalate crystals in the urine. Ethylene glycol may also be associated with central nervous system excitation, an increase in muscle enzymes and hypocalcemia. A toxicology laboratory can quickly give information as to a blood salicylate level. Of note in this patient was a history of two salicylate tablets taken in the morning for headache.

Osmolality is a reflection of the number of

molecules dissolved in a liquid. In the clinical laboratory, osmolality is usually determined by measuring the freezing point of a solution. Sodium, urea and glucose are the substances that primarily contribute to this serum osmolality. The difference between the measured osmolality and the osmolality calculated from known concentrations of major osmolar constituents of the serum is known as the osmolar gap. Using the formula shown on Figure 1, the mean serum osmolality of normal persons is 286 mOsm per kg of H_2O with an SD ± 4.2 mOsm per of kg of H_2O. Theoretical considerations indicate that a substance will significantly contribute to the osmolality of the serum only if it achieves a high blood level and has a relatively low molecular weight. In an emergency room, the serum osmolality provides a rapid, convenient measure of detecting intoxication with ethanol, isopropyl alcohol, ethylene glycol and methanol.

Table 1 shows the molecular weight, estimated lethal levels and the expected osmolalities. Thus, visual symptoms, acidosis, anion gap and unexplained osmolar forces will lead to the clinical diagnosis of methanol poisoning. Isopropyl alcohol may also cause depressed central nervous system function and unexplained osmolar gap but usually does not cause severe acidosis and will cause acetonemia with a relatively low serum glucose level. Occasional cases of isoniazid poisoning, or carbon monoxide, lead or arsenic intoxication may confuse the differential diagnosis in an alcoholic patient.

It is critical that a blood methanol level be determined as soon as possible if the diagnosis is suspected. If the clinical suspicion of methanol poisoning is high, treatment should not be delayed pending the reporting of a blood level. Methanol levels in excess of 50 mg per dl are probably an absolute indication for hemodialysis and ethanol treatment. When levels are below 50 mg per dl, ethanol treatment should be begun (or continued) and the tests repeated.

The first treatment for methanol poisoning, as in all critical poisoning situations, is to establish respiration and create an artificial airway if necessary. Emesis can be induced if the patient is not comatose, is not having seizures and has not lost the gag reflex. If these contraindications exist, then the patient should be endotracheally intubated and a gastric lavage carried out with a large bore tube. There are three major modalities of treatment for severe methanol poisoning: (1) diminishment of metabolic degradation to toxic products, (2) dialysis to enhance removal of methanol and its toxic products and to improve acid/base balance and (3) alkalinization to counteract the metabolic acidosis.

Because ethanol competes for alcohol dehydrogenase, which is responsible for metabolizing methanol to formic acid, it is essential to block this enzyme by administering the less toxic ethanol. Ethanol has a higher enzyme affinity and is preferentially metabolized by alcohol dehydrogenase. Blood ethanol concentrations greater than 100 mg per dl are probably optimal for blocking this enzyme system. The dose-dependent characteristics of ethanol metabolism and the variability induced by chronic ethanol intake require the frequent monitoring of blood ethanol levels to ensure appropriate alcohol concentrations.

With the initiation of dialysis procedures, ethanol will also be eliminated in the dialysate, requiring alterations of the dose of ethanol. Table 2 lists the approximate loading dose and infusion rates during and after dialysis in a 70-kg adult. Ethanol distributes in body water so that a loading dose of 42 grams will achieve a blood concentration of 100 mg per dl in a 70-kg patient. During dialysis, approximately 12 to 18 grams per hour should be given and after the dialysis, between 5 and 11 grams per hour. If the patient is awake or a nasogastric tube is placed, then the oral route can be utilized for ethanol by using 43 percent (86 proof) alcohol.

Alcohol may also be given intravenously, although high concentrations of alcohol are painful. A 10 percent intravenous solution is usually required. The estimates of ethanol levels given here should be verified by frequent alcohol determinations, especially during dialysis. It is generally desirable to maintain the ethanol infusion until

TABLE 2.—*The Approximate Loading Dose and Infusion Rates of Ethanol in Treating Methanol Poisoning in a 70-kg Adult*

	Loading Dose	*During Dialysis*	*After Dialysis*
Ethanol (sp gr 0.79)	42 grams	12-18 grams/hour	5-11 grams/hour
Intravenous, 10% (7.9 grams/dl)	530 ml	150-230 ml/hour	60-140 ml/hour
Orally, 86 proof (43%) (34 grams/dl)	125 ml	35-55 ml/hour	15-35 ml/hour

methanol levels are undetectable. It is also useful to remember that 1 ml of absolute alcohol contains 790 mg of ethanol (specific gravity 0.79). A 10 percent ethanol solution has 79 grams per dl and an 86-proof alcoholic beverage has 34 grams per dl.

Since folate-dependent systems are probably responsible for the oxidation of formic acid to carbon dioxide in humans, it is probably useful to administer folic acid to patients poisoned with methanol, although this has never been tested in clinical studies. 4-Methylpyrazole may also be a useful adjunct in methanol poisoning if it becomes available for human use.

With confirmation of the diagnosis of methanol poisoning and identification of a blood level higher than 50 mg per dl, hemodialysis is indicated.[19,20] Peritoneal dialysis has been shown to be less efficacious than hemodialysis.[21] In the past few years, sorbent-based regeneration hemodialysis systems (REDY) have become available as a method for routine use in patients with chronic and acute renal failure. Because the system is readily portable, is relatively small in size and has a small dialysate volume, this system can be easily tailored to an individual patient. However, the sorbent-based hemodialysis systems have been shown to be ineffective in the treatment of methanol poisoning.[22]

Because of the profound metabolic acidosis in methanol poisoning, treatment with bicarbonate therapy may be necessary. It is very unlikely that the acidosis itself causes damages or alters the outcome of the visual disturbances. Quantities of bicarbonate to be administered should be adjusted based upon estimated sodium intake, concern for potassium balance and careful monitoring of cardiovascular status.

A special problem would result if the patient had a relatively low methanol level but visual symptoms. In this situation the laboratory test for methanol itself should be repeated and confirmed with osmolality estimates. If visual impairment is present, hemodialysis should be begun independent of the methanol level.

Discussion of Case

Our patient today represents a sporadic case of severe methanol intoxication. Of note was her occupation as a pathology resident and the onset of visual symptoms while carrying out an autopsy. One of the early questions in this case involved the possibility of formaldehyde or formalin intoxication. This would seem unlikely in this case because formaldehyde and formalin are so injurious to mucous membranes, and there were no such symptoms. Methanol inhalation in the pathology laboratory also seemed unlikely in that exposure during the relatively brief time of the autopsy would not account for a blood level of methanol of 140 mg per dl. However, permissible exposure levels of methanol of 200 ppm may be exceeded by persons working with methanol and does represent a potentially serious occupational hazard. Health hazards of chronic formaldehyde exposure remain to be determined.

The initial presentation with eye symptoms in our patient is classic. The history was confused by the ingestion of two aspirin early in the morning for a headache and the 12-hour delay in the onset of her symptoms. This delay may be explained in part by her simultaneous ingestion of ethanol with her evening meal. The laboratory findings in this case illustrate an anion gap and an osmolar gap. Toxicology laboratory levels were reported and institution of ethanol administration and hemodialysis was prompt. Of special note are the normal funduscopic evaluations. The unusual method of administration of the methanol in this case is under police investigation.

Conclusion

Methanol intoxication in sporadic fashion is an uncommon but extremely hazardous poisoning. It is likely that methanol will be a versatile fuel with increasing usage in our energy-conscious society. Proposed uses of methanol should be weighed against potential hazards. Methanol is likely to become a competitor with petroleum products because it is economically attractive to derive methanol from otherwise unused or discarded sources. Since the toxicity of methanol is serious and its mortality unacceptable, every effort should be made to monitor and protect workers exposed to methanol and common sources of methanol such as windshield de-icer sprays and canned heat. These products should have appropriate labeling, and packaging should be designed to protect children. Our desire to find safer fuel sources should be tempered with the recognition of the hazard so that delivery systems of the material are protected, perhaps by adding an emetic to methanol or making sure that antisiphoning methods are employed. The blind drunk is, fortunately, an uncommon event. As in the case discussed today, methanol intoxication requires immediate diag-

nosis, institution of treatment before laboratory confirmation and a thorough appreciation of pharmacotoxicology.

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Suppression of Immunity by Cytotoxic Agents?

WHAT ABOUT cytotoxic agents? Swanson and Schwartz, years ago at Tufts New England Medical Center, showed that if you take azathioprine and mercaptopurine and give those drugs to a normal person you will significantly suppress delayed hypersensitivity and cell-mediated immunity. And these are drugs that we use in patients with Hodgkin's disease—and they already have a defect from their underlying disease. Could corticosteroids or cytotoxic agents themselves predispose to infection? After all, we have patients—say with severe asthma—receiving high doses of corticosteroids for many years, or relatively high doses. Do they get infected? The answer is not much more than the general population.

—JACK S. REMINGTON, MD, *Palo Alto, California*

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Important Advances in Clinical Medicine

Epitomes of Progress — Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Diagnostic Ophthalmic Ultrasonography

DIAGNOSTIC ULTRASONOGRAPHY, of great value in clinical ophthalmology, is used frequently to differentiate intraocular lesions, particularly in cases of retinal detachment, tumor or vitreous hemorrhage. When the posterior segment cannot be seen because of corneal opacity, cataract or a miotic pupil, ultrasound testing provides the most dependable method for investigation. Contact B-scan units are more practical for posterior segment pathology; however, the lens, iris and ciliary body can be studied by holding the transducer in a water bath placed over the eye. The B-scan device provides a visible cross-section of the eye that is helpful in orientation, and the A-scan unit gives additional details of tumors and assists in the differential diagnosis of retinal detachment and vitreous membranes. Both A-scan and B-scan ultrasonographic units are highly reliable in diagnosing intraocular tumors.

A-scan and B-scan ultrasonography is useful for detecting and localizing foreign bodies. However, in some cases where the foreign body is small or located near the scleral wall, the findings may not be conclusive. Therefore, standard x-ray views of the eye and orbit should be obtained if a foreign body is suspected, and, in many cases, the traditional method of x-ray localization is still indicated.

B-scan ultrasound testing is of remarkable value with cystic orbital lesions such as mucoceles and dermoids. A-scan and B-scan ultrasonography can also be very useful in cases of endocrine exophthalmos, where enlargement of the extraocular muscles is frequently found. Pseudotumor and other solid orbital tumors can be detected with A-scan and B-scan ultrasound testing. Recent refinements of computed tomography—both computed axial tomography (CAT) and computed coronal tomography (CCT), have established that this latter technique is of greater value in demonstrating some orbital tumors. Standardized A-scan ultrasound testing, however, can be of more assistance in determining the type of tumor once the size and location are known.

A-scan ultrasound equipment has been designed and calibrated for the accurate measurement of axial lengths to calculate lens power. Measurements are made by photographing the A-scan with a superimposed scale that is calibrated in micro-

seconds. The millimeters of axial length can be determined by using tables that take into account the speed of sound transmission in aqueous, vitreous and the lens. A-scan units having digital read-out screens are much easier and quicker to use, although the accuracy of both methods is comparable.

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Major Ocular Trauma

OCULAR TRAUMA remains one of the leading causes of blindness, particularly in younger persons. The results of treatment of injuries to the anterior structures of the eye have improved dramatically primarily because of the use of microsurgical techniques and postoperative topical steroids. However, injuries involving the posterior portion of the eye, such as the vitreous and retina, continue to have a poor prognosis because of the high incidence of retinal detachment.

A posterior penetrating eye injury is often complicated by vitreous hemorrhage, which is a potent stimulus to inflammation. The reparative process is characterized by proliferation of fibroblasts and, as in other parts of the body, contractile myofibroblasts, which are cells with smooth-muscle characteristics. While this repair process is beneficial for the skin and other organs, it can be harmful to the eye, primarily because of the anatomical relationship of the vitreous and retina anteriorly. The myofibroblasts use condensations of the incarcerated vitreous as a scaffold to form transvitreal and epiretinal membranes, which later contract and cause traction on the retina, eventually leading to traction retinal detachment.

With pars plana vitrectomy, this proliferative process may be interrupted and many cases, previously considered inoperable, can now be salvaged. Vitrectomy is carried out using a small cutting and sucking instrument of less than 1 mm in diameter that is introduced into the vitreous cavity just anterior to the retina. An infusion of physiological solution maintains the intraocular volume and, thus, complex manipulations inside the eye are possible.

Penetrating ocular injuries must be repaired promptly. If the presence of an intraocular foreign body is suspected preoperatively, it must be identified using x-ray studies and then localized by computerized tomography (CT scan) or ultrasonography. At the time of primary repair, corneal and scleral lacerations are sutured, using microsurgical techniques. A severely disrupted lens may be removed at the same time, but if the injury involves the posterior ocular structures, the ophthalmologist should confine the primary repair to meticulous surgical wound cleansing and precise closure. An extensive posterior vitrectomy is delayed until the time of the second reconstruction, some 7 to 10 days after injury. By this time, the risk of intraocular bleeding has lessened and alterations in vitreous anatomy make vitrectomy technically easier.

The surgical objectives at this stage are to remove opacities such as vitreous hemorrhage or a cataractous lens, to peel and segment vitreous traction membranes, to remove nonmagnetic or impacted intraocular foreign bodies and to identify and treat retinal holes or detachment. If the retina is detached, the infused fluid in the vitreous cavity may be exchanged with air or a sulfur hexafluoride (SF_6) gas/air mixture to provide an effective retinal tamponade.

Vitrectomy has become an established mode of treatment for severe ocular injuries. While primary repair remains the domain of a general opthalmologist, vitrectomy is a time-consuming operation, requiring complex instrumentation and experienced personnel and is best done in a center with special expertise in vitreous procedures.

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Danger With Eyedrops

EYE SOLUTIONS, suspensions and ointments are the most common methods of delivering medication to the conjunctiva, cornea and anterior chamber. These medications range from simple decongestants to potent antimicrobial or corticosteroid drugs. Eyedrops can be crucial in the treatment of serious eye disease; however, their misuse can be harmful to the eyes.

For proper administration of eyedrops, the patient should look up with the head tilted back slightly. When the lower lid is pulled away from the eyeball, the drop is placed inside the lower lid and the patient is advised to blink gently *without* squeezing the lids closed. The patient should blot

away only that medication which runs out of the eye, and maximum absorption is thus achieved. The tip of the dropper should not touch the eye or lids.

Simple decongestant drops are widely used because the medication is available without prescription. Occasional use for itching, burning eyes is acceptable, but routine use is to be discouraged because rebound hyperemia and sensitivity reactions to the medication or preservative may result.

Antimicrobial (for example, bacterial, viral or fungal) medications should be ordered only when clearly indicated. These drops are given for infection and, in cases of severe conjunctivitis or corneal infection, sometimes must be administered as often as every hour, on a 24-hour basis. Toxic and hypersensitivity reactions are common.

Corticosteroid eyedrops can be critical in treating ocular inflammations such as iritis. These drops can cause devastating eye disease, however, such as blinding glaucoma and cataracts. Steroids also can facilitate the development of viral, bacterial or fungal corneal disease. Because the damage done by treatment with corticosteroids can far outweigh any anti-inflammatory benefit gained by adding a steroid to an antibiotic, nonophthalmologists should use antimicrobial agents alone, without the addition of steroids.

Eyedrops are best dispensed in small volumes. Also, the medication should be discarded after the treatment program or the expiration date, and the drops should not be used by another person.

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Diabetic Retinopathy

DIABETIC RETINOPATHY is the second leading cause of blindness in the United States. The duration of the disease is the most important factor in determining the presence of observable retinal disease. By the age of 50 years a person with diabetes is approximately 23 times more likely to become blind than a person without this disease, and once blindness develops the average life expectancy is less than six years. Fewer than 25 percent of blind diabetic persons survive ten years.

The fundus findings in nonproliferative or "simple" diabetic retinopathy include microaneurysms, retinal hemorrhages, soft exudates (ischemic infarct), and hard exudates (lipid). Macular edema may develop from leaking retinal vessels and is the main cause of the loss of vision. Proliferative or "malignant" diabetic retinopathy develops if new retinal vessels (neovascularization) appear, and secondary complications of vitreous hemorrhage and retinal detachment also may lead to loss of vision.

The cause of new retinal vessels continues to be speculative, although investigation suggests that a diffusable vasoproliferative factor, produced by ischemic retina, may stimulate new vessels to develop.

Fluorescein angiography—the injection of fluorescein dye into the antecubital vein, with collection of the information on framed photographic film—plays an important role in determining the extent of fundus vascular pathology in diabetic retinopathy. Specifically, areas of vascular nonperfusion, leaking blood vessels and early retinal neovascularization can be identified.

The Diabetic Retinopathy Study (DRS) Research Group, sponsored by the National Institutes of Health, has reported an increased risk of severe loss of vision developing within two years in association with the following factors: (1) presence of vitreous or preretinal hemorrhage; (2) development of new vessels; (3) location of new vessels on or near the optic disc, and (4) severity of the neovascularization.

Light photocoagulation of the retina remains the accepted treatment for control of proliferative diabetic retinopathy when the "high-risk" factors identified by the DRS are present. Photocoagulation is also beneficial in treating some cases of vision loss due to macular disease. Fluorescein angiography data provide the basis for case selection in treatment of macular disease with laser photocoagulation. Panretinal photocoagulation may be beneficial in the control of rubeosis iridis (formation of new vessels on the surface of the iris), a condition that can lead to secondary glaucoma as a complication of diabetic retinopathy.

Nonresolving vitreous hemorrhage and traction retinal detachment involving the macula may be treated by pars plana vitrectomy, which removes blood and vitreous traction bands. Vitreous surgical procedures are usually reserved for longstanding vitreous hemorrhage; however, a national collaborative clinical trial is studying the role of such procedures in eyes with vitreous hemorrhage of shorter duration and in eyes with clear media and severe proliferative retinopathy. Vitreous op-

erations may improve or stabilize vision in diabetic patients with other severe eye complications; however, careful consideration must be given because of a high incidence of surgical complications.

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Extended Wear Contact Lenses

EXTENDED WEAR CONTACT LENSES are soft contact lenses that can be worn continuously for weeks to months. They offer the same optical advantages as conventional contact lenses but are removed only for cleaning. If a complication occurs, however, they can be easily taken out, which is a distinct advantage over intraocular lenses. The Cooper Permalens, Hydrocurve and Hyer-Schulte Sauflon lenses are approved for aphakia, and the Hydrocurve II-55 and Permalens are approved for myopic (near-sighted) extended wear.

Extended wear lenses are indicated only for those patients who cannot wear conventional contact lenses (hard or soft) or thick cataract glasses. Patients who are unable to insert or remove conventional contact lenses or who cannot adjust to glasses may be considered candidates for extended wear lenses. However, patients with tear deficiencies or chronic eyelid infections who are prone to complications should not wear these lenses.

Compared with conventional soft lenses, extended wear contact lenses are more successful because they transmit more oxygen to the cornea due to a higher water content or a thinner lens design. The success rate for myopic and aphakic patients wearing these lenses has been reported to be more than 90 percent and 70 percent, respectively. Ninety percent of myopic and 78 percent of postcataract patients achieve a vision of 20/30 or better.

The most common complications have been lens deposits, lens breakage and loss, corneal edema and neovascularization. Corneal infections have been a rare problem.

To minimize such complications, patients are instructed to see their ophthalmologist if pain, redness or decreased vision occurs.

In the future, we can expect high-oxygen permeable lenses, such as those made of silicone or cellulous acetate butyrate, to produce a higher success rate, fewer complications and better levels of visual acuity.

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Orthokeratology

ORTHOKERATOLOGY IS AN optometric procedure in which patients are specially fitted with hard contact lenses to induce a flattening in the corneal curvature and thereby reduce myopia (near-sightedness). After four to six weeks new, flatter lenses are fitted to further the flattening process. Lenses are refitted in the same manner for 18 to 30 months until the patient's near-sightedness has been eliminated or until no further changes can be induced.

Orthokeratologists, representing a small minority of optometrists, claim the procedure is capable of correcting certain amounts of near-sightedness and that when contact lenses are finally removed, the visual acuity will be improved. They also claim that the procedure has a scientific basis, is predictable and has few complications. Although many patients are required to wear "retainer" contact lenses, designed to maintain the induced changes, orthokeratologists state that patients can go without contact lenses for days to weeks without a regression of their visual acuity.

Two scientific studies have not substantiated the orthokeratologists' claims. Both have shown the following: (1) the procedure does not have a scientific basis and is not predictable, (2) the amount of myopia which can be corrected is less than 2 diopters, (3) stabilization requires more than 20 months to achieve, and when the contact lenses are removed, the corneas return to their former shape and visual acuity returns to previous levels and, most important, (4) the patient's best possible unaided visual acuity does not always return immediately on removal of the contact lenses. In some patients the lenses have to be removed for 12 to 36 hours to achieve any improvement in unaided visual acuity. Futhermore, the quality of the visual acuity without the contact lenses is less than that with glasses or standard contact lenses. For example, some patients stated

that their vision was distorted—as though they were looking through a dirty windshield or a fish bowl. Based on a short-term evaluation, both studies concluded that the procedure has no permanent risks to the cornea but that it also has nothing to offer a patient.

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Lacrimal Repair

THE PERMANENT PROBLEM of tearing secondary to damage to the lacrimal excretory system is unnecessary because of advances in techniques of surgical repair. Previously, traumatic or congenital disruption of the lacrimal canaliculi was generally considered nonrepairable. Older methods of repair, using a steel rod or a "pigtail probe," often caused considerable discomfort to the patient and damage to fragile tissues.

The use of indwelling soft silicone tubing, as advocated by Quickert, combined with microsurgical direct anastomosis has improved the prognosis for functional healing. These soft tubes are passed through the upper and lower canaliculi, lacrimal sac and lacrimal duct and are fastened where the lacrimal duct exits on the lateral nasal wall. Jones and associates have demonstrated that tears may flow through either the upper or lower canaliculus and, in some persons, the flow may be better through the upper passage. Thus, ophthalmologists now tend to repair a laceration of either canaliculus with the long-term indwelling tubes.

The newer Guibor model is easier to insert because the tubing is swaged onto a metallic probe. The tubes are tolerated for extended periods while a permanent fistula forms and are easily withdrawn from the nose when no longer needed. Often the patient is unaware of tearing while the tube is in place because the tears pass along the outside surface of the silicone tubing. The use of microscopy to locate the vestigial tract or the severed end of the canaliculus and also to facilitate surgical repair has greatly enhanced the success rate.

The silicone tubes are also used in selected cases of chronic tearing which otherwise would need more extensive surgical repair such as a dacryocystorhinostomy. The distinct advantage of the former technique is that the patient does not require a permanent prosthetic device since the silicone tubing is removed when no longer needed.

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Iridology

ALMOST A CENTURY has passed since Ignatz Peczely, an obscure Hungarian physician, enunciated basic principles of physical diagnosis by examination of minute surface topography of the iris. In spite of the manifest absurdity of the conclusions drawn from such examinations, the cult of "oculodiagnosticians" flourished thereafter, particularly in Central Europe. Early in this century, iridiagnosis (later iridology) was introduced in the United States, and it has been with us ever since. It is now primarily, though not exclusively, within the domain of a small but growing group of chiropractors. Magazine articles, television programs and newspaper advertisements have heightened public awareness of the availability of this supposed diagnostic method. An attempt to achieve further respectability for iridology has been made by wrapping it in the mantle of holistic health.

For an iridologist, every organ of the body is represented on an iris chart that is superimposed on a patient's iris like a template before interpretation. Not all iris charts are the same. Practitioners appear free to modify their charts at will. It is disconcerting to realize that one iridologist's scrotum might be another's scapula. Every fleck, spot, color variation, elevation and depression, all real or imagined, is presumed to have diagnostic significance. *Modern* iridology employs an anterior segment camera. An enlarged color photo of the iris is obtained for analysis. The descriptions and interpretations accompanying such photos indicate to this writer that an active imagination is an essential prerequisite for the practice of iridology.

It is not difficult to refute the tenets of this pseudoscience and the diagnostic conclusions it attempts to draw. The iridologist makes no allowances for stabilization of pupillary size, changes that may alter iris topography significantly. Similarly, a diseased iris is not recognized as such. Instead, the abnormal changes are interpreted as bodily disorders. It is unsettling to reflect that, according to iridology's precepts, some cases of

essential iris atrophy (iridocorneal syndrome) should indicate absence of the heart or a substantial part of the brain. For one iridologist, an arcus senilis is a ring of sodium deposited in the iris, for another it is an indicator of anemia or enervation. The owner of a blue iris is blessed with a promise of longevity. Look carefully, though! If the blue is faintly coated with white, the blessing is revoked because the whitish layer represents an accumulation of harmful acids. Let the owner of a vertically oval pupil prepare to make peace with his Maker for it is a sign of imminent death. If both pupils are so shaped, do not bother for there is not enough time.

A distinct flavor of the medically medieval pervades standard treatises on iridology. One is likely to encounter such curious entities as uterine catarrh, prolapse of the transverse colon, abdominal plethora and a lymphatic-rheumatic-tubercular constitution.

Nutritional balance emerges as the handmaiden of iridology. There are iris drug spots and cramp rings to be erased, toxins to be flushed, overactive and underactive glands to be set right. Nutritional correction is the primary tool and, not surprisingly, iridologists often have the appropriate food supplements available for sale to achieve these worthy ends. Periodic examinations of the iris are required to determine if and when a state of true health has been restored.

Iridologists have been quick to grant that theirs is not the only technique available for the diagnosis of disease. All of them have argued that it is as valid as most and has on occasion proved superior to some. The truth of this contention was tested in a recent study, which has emerged as the first genuine piece of scientific research on this subject. Three ophthalmologists and three iridologists viewed iris photographs of 143 patients. Of these patients, 48 had kidney disease and 95 did not. No other clinical information was made available to the viewers. The iridologists demonstrated no statistically significant ability to identify the victims of kidney disease.

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EDITORIALS

Competition in the Health Care Enterprise

It seems now to be conventional wisdom that more competition is needed in the health care enterprise and the intention of the new federal administration appears to be to foster it. Many seem to look upon this as something new and even long overdue. But in many ways the health care enterprise is and has always been highly competitive. Certainly research workers compete for funds and with each other in the race to reach a new discovery. The pharmaceutical industry, which is essential to the health care enterprise, is highly competitive—although now somewhat hampered by what seem to many to be unnecessarily stringent federal regulations. Doctors themselves may be regarded as highly successful competitors, having competed successfully at every step of a long and often arduous training, and after they enter practice their success depends considerably upon the reputation they can earn in the competitive world of patient care. It seems likely that this competitiveness which is inherent in the health care enterprise is what has made possible the most advanced and also the costliest health care in the world.

If one goes back to the turn of the century or before, competition in health care was rampant and unharnessed. There were many more medical schools than there are today and most of them were not very good. There were practitioners of every description. Licensing standards for health professionals and other elements of the health care enterprise were either nonexistent or inadequate in terms of reasonable standards of quality. Largely through the efforts of the medical profession, beginning with the Flexner Report in 1910, some order was brought into the chaos of medical education and patient care, and professional accreditation and certification which met professional standards were the tools that were used. This process of peer review and quality control by the profession has continued to this day.

In recent years there have been perceptions of a medical trust through which the medical profession (usually referred to as the AMA) seeks to control prices and to restrict competition. What appears to have happened is that as the profession began to exercise stronger professional control over quality this became viewed as unwarranted and inappropriate control over the business or industry of health care. There is now clear evidence that all three branches of government are responding to these more recent perceptions and are acting to weaken professional control over the quality of care rendered in the health care enterprise through agencies of the executive branch (the Federal Trade Commission, for example), through the legislature (by increasing the scope of permitted practice of many health professionals other than physicians) and through case law as this continues to be established by the courts.

No editorial by this or any other writer is going to change all of this. It still remains to be seen what even more competition in practice will do to the cost of health care. But of genuine concern is what it, together with substantial reductions in funding for research, health professional education and patient care services, will do to the quality of health care services rendered to the citizens of this nation.

There is no group more qualified to pass judgment on excellence or the lack of it in patient care than the medical profession. If competition in the health care enterprise is fostered at the expense of reasonable quality controls by the medical profession, the end result could be a return to something like the conditions of 1900. However, there would be considerably more dangers to the public because modern technology is infinitely more capable of doing both good and harm than was the technology available at the turn of the century. It is to be hoped that somehow the medical profession will find ways to retain and strengthen its

essential grip on the quality of care rendered by the health care enterprise to the people of the nation. This will probably not be easy, but it must be accomplished. It far overshadows in importance the hoped for benefits, to both patients and public, of yet more competition.

—MSMW

Helmets for Motorcyclists

In this month's issue, Luna and his co-workers have documented the efficacy of wearing a helmet while riding a motorcycle. Of the various trauma prevention programs, mandatory helmet usage is among the least difficult to implement and carry out. For example, when compared with such other approaches as handgun control, removing drunk drivers from the highways or legalization of drugs, it is uncomplicated and easy.

In 1967 a federal highway safety standard required that all states enact and enforce mandatory helmet laws. In 1976 Congress passed a law revoking federal sanctions against states not complying with the helmet standard. During the time the sanctions were in force (1965 to 1976) the number of fatalities per 10,000 motorcycles fell from 12.8 to 6.5. Between 1976 and 1979, there were 27 states that either repealed or substantially weakened their helmet use laws. This resulted in a 46 percent increase in total motorcycle deaths.

In a study done in California by Harry Hurt,[1] 60 percent of motorcycle riders were not wearing safety helmets at the time of their crashes. Of this group, 26 percent said they did not wear helmets because they were uncomfortable and inconvenient and 53 percent had no expectation of crash involvement. Of those sustaining head injuries, 14 percent were wearing helmets at the time of the crashes; 23 percent of the fatally injured riders were wearing helmets but only 1 helmeted rider died of head injuries. Hurt concluded that the use of a safety helmet is the single most critical factor in the prevention or reduction of head injury.

In a study of 71 motorcyclists admitted to Denver General Hospital[2] only 38 percent were covered by commercial insurance or workers' compensation. It was found that 59 percent of the unpaid bills were borne by taxpayers. The Maryland Institute for Emergency Medical Services[3] carried out a study involving 65 patients. Of these patients, 40 percent did not pay their bills; the bills averaged $11,038. Twenty-five percent were uninsured and the combined unpaid bills amounted to $433,200, all of which had to be absorbed by taxpayers.

Motorcycle helmet opponents argue that helmets reduce peripheral vision and thus contribute to crash risks. Studies done by the National Highway Traffic Safety Administration showed that peripheral vision was found to be restricted in less than 3 percent of currently available helmets. The same opponents argue that helmets make it difficult for cyclists to hear. In the study done by Hurt, helmets did not lower the cyclists' ability to distinguish critical traffic sounds. Helmets are said to contribute to neck injuries. In the California study only 4 of the 980 head and neck injuries were attributed to safety helmets.

The data supporting the use of safety helmets by motorcyclists seem overwhelming. Clearly, helmets reduce death and head injuries. For those who continue to oppose mandatory motorcycle helmet laws a fundamental question must be answered: When do societal rights become more important than individual rights? The answer seems self-evident.

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Noninvasive Methods for the Study of Patients With Coronary Heart Disease

Elsewhere in this issue, Dr. Victor F. Froelicher has assembled reports on recent advances and current status of new noninvasive methods of evaluating patients with coronary heart disease. Motivation for these developments, which often provide less precision of anatomical details, is the alleged risk of vascular and cardiac complications induced by catheterization techniques. To put this into perspective, and disregarding the ever increasing financial costs of all methods, there is a small but definite clinical cost of two to three fatalities per thousand patients studied invasively with use of nonoxygenated, hyperosmolar contrast media to obtain visualization of morphologic de-

tails, particularly in high-risk, severely ischemic patients with heart disease. Morbidity from thrombosis requiring surgical treatment, hematoma from bleeding at arteriostomy or venostomy sites, and other less frequent miscellaneous complications such as microembolism to the cerebral or retinal circulations, are no less frequent problems. Thus, there is justification for continued research efforts to develop and eventually to substitute noninvasive methods, but the clinical justification to rely on them varies with value judgment of cost-effectiveness. Assessment of these aspects emerges slowly from the continued progress of many investigators employing diverse methods.

The salient clinical advantages, for these purposes, of electrocardiography (ECG) are cited by Dr. Ary Goldberger. In addition to the known strengths and weaknesses of conventional "low frequency" electrocardiography, he offers some observations about the correlations with inverted anterior T waves, which normalize with acute ischemia or persist in the presence of severe regional vascular stenosis and abnormal wall motion by ventriculography. In the former instance the potential contribution of posterior wall ischemia in the presence of inferior T wave inversion in the illustration, is neglected. Several causes of non-infarct-induced Q waves are cited to emphasize the limitations of this hallmark of infarction. Likewise other causes of ST elevation and T wave inversion are cited. Accordingly the need for consideration of all pertinent clinical information is properly emphasized before reliable interpretations of ECG changes may be derived. With improved technology, high frequency ECG information is also available, but the information described is meager and does not reflect prior contributions of other investigators. The substantial change in late as well as early depolarization of the ventricle with inferior infarction has been previously reported.

Dr. Tubau describes clinical experience at the Montreal Heart Institute with multichannel (14 leads) ECG recordings of exercise tests. All tests *were,* rather than *had to be,* considered maximal by exceeding at least 85 percent of the age-predicted maximal heart rate when the Bruce protocol for such testing was arbitrarily and (in the opinion of this reviewer) inadvisably modified. Interpretation of responses to exercise in 87 patients with angina reflects obsolete classification of "positive" versus "negative" responses with respect to ST depression but reveals awareness of the importance of disease prevalence in various subgroups of patients and inadequacy of left ventricular function as appraised by duration of such exertion. Formulation of posttest *risk* (relative certainty or clinical confidence in diagnosis?) as product of prevalence of disease and likelihood ratio represents a more sophisticated assessment, albeit limited by the major preoccupation with ST depression, without consideration of its major determinants, namely cardiac dimensions and pressure-rate product. Yet the study is consistent with various observations that some system for multiple leads, either in graphic arrays (or, alternatively, electrically synthesized with spatial orientation) provides more useful information. The majority of 118 patients with previous myocardial infarction had multivessel coronary artery disease. Abnormal ECG responses identified from 80 percent to 96 percent of patients, in proportion to severity of symptoms with inferior infarction and multivessel disease; exercise testing was more useful in those with minimal symptoms. Somewhat lower yields were obtained in patients with previous anterior infarcts. ST elevation did not augment sensitivity of test response; this stands in contrast to other data indicating a poor prognosis for survival without subsequent cardiac events. This does not emerge from a study based solely upon immediate diagnostic correlations with arteriography. The conclusions of the author are valid but unfortunately disregard other equally available, and at less expense, blood pressure responses to exercise testing.

Advantages and limitations of M-mode echocardiography are cited by Dr. Costello. Multiple axis, two-dimensional echocardiographic techniques have greatly extended evaluation of size and mobility of cardiac chambers, walls and valves in the patient at rest. Ejection fractions are more reliably appraised than left ventricular volumes in systole and diastole because of tangential viewing and underestimation of circumference. Of greater interest, regional wall contraction abnormalities and pseudoaneurysms may be detected. Serial observations of acute infarction indicate the prognostic importance of cardiac dilatation. Even septal perforation and papillary muscle rupture have been detected; possible reliable assessment of stenosis of left main coronary arteries will emerge also.

Unfortunately accurate echocardiographic displays in response to the stress of strenuous exer-

cise, where the need for such assessment is substantial, is limited by the associated hyperpnea and mobility of the patient under such circumstances.

These needs are approached by use of two radionuclide imaging techniques discussed by Dr. Tubau. First, the time activity curve of the first pass of a radionuclide bolus through the left ventricle permits assessment of ejection fraction from the average end-diastolic and end-systolic counts for a few successive heart beats. This estimate correlates with that of biplane ventriculography. Superimposing images of short duration from successive heart beats provides an approximation to ventricular volumes and therefore estimation of changes in volumes wiih the heart cycle. Such estimates permit derivation of cardiac output similar to those obtained by indicator dilution methods. Output may also be estimated from the first pass of the radionuclide by integration of the gamma camera image of the heart.

Another and more accurate radionuclide technique is use of a stable radionuclide such as technetium 99m linked to albumin or red blood cells that remains in the circulation for a few hours. This requires counting of 300 or more successive heart beats for each assessment, but this evaluation may be repeated periodically for several intervals. Despite assumptions about adequacy of normalization of the left ventricular counts, of rate of radioactive decay and of attenuation as influenced by various tissue factors and distance from the gamma camera, continuing efforts are made to estimate ventricular volumes and therefore cardiac output. Because of established differences with contrast ventriculographic volumes correction factors are needed. Experience to date seems to emphasize limitations rather than advantages, although relative changes in volumes needed for ejection fraction are more likely to be representative.

These reviews would be more helpful if emphasis were placed on how these methods improve the clinical decision-making processes. Yet the concluding remarks of the conference coordinator reflect a contemporary clinical assessment. Another method, namely that of thallium imaging to assess dynamic changes in myocardial perfusion due to ischemia is not assessed. Guidelines regarding optimal utilization in terms of clinical indications would be useful to referring physicians. Perhaps a similar review in another decade will include the advantages and limitations of positron emission tomography, which offers the potential, albeit at considerable equipment and technological expense, of evaluating left ventricular function, coronary blood flow and myocardial metabolism globally and regionally by other radionuclide imaging techniques.

Meanwhile for physicians concerned about more predictive assessment of risks of primary or secondary events due to coronary heart disease in middle-aged ambulatory men observed in routine clinical office practice, insights from the recently published noninvasive exercise studies of the Seattle Heart Watch offer considerable promise at minimal expense.[1-4]

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CASE REPORTS

Refer to: Leimbach WN Jr, Marsidi I, Leininger NR, et al: Aortic stenosis and intestinal angiodysplasia—A case of gastric involvement. West J Med 135:139-142, Aug 1981

Aortic Stenosis and Intestinal Angiodysplasia

A Case of Gastric Involvement

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THE ASSOCIATION OF aortic stenosis with recurrent gastrointestinal bleeding was first suggested by Heyde[1] and then Schwartz in 1958.[2] Subsequent reports have described arteriovenous malformations of the lower gastrointestinal tract (predominantly of the right side of the colon) as the site of hemorrhage in patients with aortic stenosis.[3-5] Recently, angiodysplasia of the stomach or duodenum has been reported in patients with aortic stenosis as a cause of recurrent unexplained massive upper gastrointestinal bleeding.[6,7] While angiography was often necessary for identification of the lower gastrointestinal lesions, endoscopy has been shown to be of value in the identification of upper gastrointestinal lesions. Therefore, aortic stenosis associated with angiodysplasia can include both upper gastrointestinal lesions, as well as the predominantly recognized right-sided colonic lesions. In patients with unexplained recurrent gastrointestinal bleeding and aortic stenosis, an intensive evaluation should be carried out of both the lower and upper gastrointestinal tracts for such lesions.

Presented is a case of a patient with aortic stenosis in whom gastric angiodysplasia caused recurrent massive upper gastrointestinal bleeding.

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Report of a Case

A 71-year-old man presented to the Iowa City Veterans Administration Medical Center with a two-year history of recurrent hematemesis. Over the previous six months there had been six episodes of gastrointestinal bleeding, all requiring admission to hospital and transfusions of at least 2 units of blood. Findings on upper gastrointestinal x-ray studies had been unremarkable. A barium enema had shown diffuse diverticulosis, and endoscopy during his fifth hospital stay failed to show a source of gastric bleeding. Despite treatment with cimetidine and antacids there was massive upper gastrointestinal bleeding from an unidentifiable source. The patient was again admitted locally, given 8 units of packed red blood cells, and transferred to the Iowa City Veterans Administration Medical Center.

On admission the vital signs were stable with mild orthostatic hypotension. He had a grade 3-4 systolic ejection murmur loudest at the base but heard throughout the precordium and in both carotids. There was a moderate delay in the upstroke of the carotid pulse. On examination occult blood was found in the stool. The hematocrit was 37.7 percent and the hemoglobin was 12.6 grams per dl. A coagulation profile was within normal limits. An electrocardiogram was significant for left ventricular hypertrophy with strain and evidence for an old anterior myocardial infarction. An isotope ventriculogram showed resting and exercise ejection fractions of 72 percent and 57 percent, respectively. An x-ray study of the chest did not show cardiomegaly, but did show aortic calcification. X-ray examination of the upper gastrointestinal tract was remarkable for two duodenal diverticula. A barium enema study showed numerous diverticula. Upper gastrointestinal panendoscopy showed a slightly raised erythematous lesion on a rugal fold of the greater curvature which was not friable or bleeding and which measured about ½ to 1 cm (Figure 1). Repeat endoscopy done three days later showed the lesion unchanged. However, a similar smaller lesion, about 2 mm, near it was also observed. On celiac and superior mesenteric artery angiography, only an accumulation of contrast material along the greater curvature of the stomach, consistent

with an acute blood loss, was noted in the area of the endoscopically seen lesion (Figure 2).

The patient was taken to surgery for a partial gastrectomy. Gross inspection of the segment of removed stomach showed the two sharply demarcated hyperemic hemorrhagic lesions seen at endoscopy, both at the apex of otherwise normal appearing rugal folds. Microscopically, the vessels in the underlying submucosa were increased in number and in caliber, and extended into the mucosa (consistent with arteriovenous malformations) (Figure 3). Similar vascular changes were present, but to a lesser degree, in areas of the gastric mucosa distant from the lesions.

Four days postoperatively, recurrent upper gastrointestinal bleeding developed. The patient was taken back to surgery for a complete gastrectomy. On microscopic examination of several different areas of the remaining section of the stomach, similar large congested submucosal blood vessels consistent with angiodysplasia were seen. These areas of angiodysplasia were not grossly evident on the mucosal surface. No other bleeding site was identified at operation. Postoperatively, the patient remained free of bleeding. Five weeks later the patient died of sepsis. An autopsy study showed severe calcific aortic valve stenosis and an abdominal abscess. Examination of the remaining gastrointestinal tract failed to show additional areas of angiodysplasia.

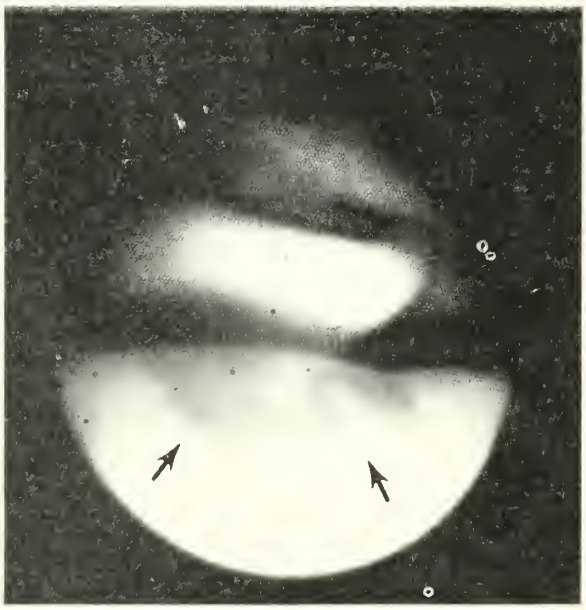

Figure 1.—Endoscopic picture showing the ½- to 1-cm slightly raised erythematous lesion on a rugal fold of the greater curvature of the stomach. Microscopic examination of this lesion from surgical specimen showed angiodysplasia.

Discussion

Heyde[1] and then Schwartz[2] in 1958 first suggested a possible increased incidence of idiopathic massive gastrointestinal bleeding in elderly patients with aortic stenosis. Williams[8] reviewed the records

Figure 2.—Celiac arteriogram shows only an accumulation of contrast material along the greater curvature of the stomach in the area of the endoscopically seen lesion. The arteriogram suggests an acute blood loss but fails to confirm the diagnosis of angiodysplasia.

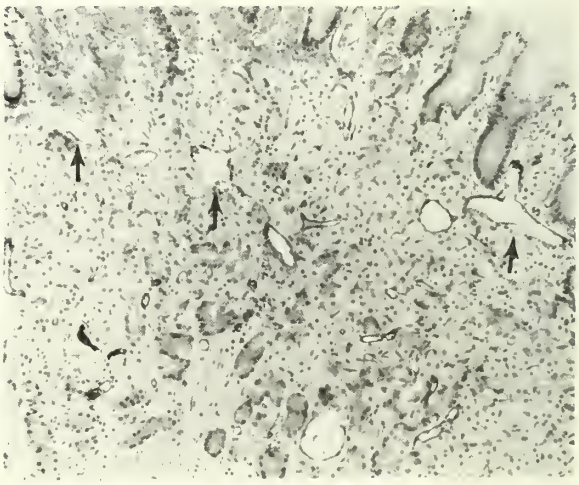

Figure 3.—Stomach biopsy specimen of an area of angiodysplasia. Note the vessels in the underlying submucosa are increased in number and caliber. (Hematoxylin and eosin stain; reduced from ×125.)

of 1,443 patients with gastrointestinal bleeding and found that in 93.5 percent of the cases there was a demonstrable cause for the bleeding. There was not a significantly higher incidence of aortic stenosis in this group of patients than in a group of matched controls (5 percent versus 4.4 percent). However, in the remaining 95 patients (6.5 percent) in whom the source of bleeding could not be found, 24 (25.5 percent) had aortic stenosis. This represented a significant increase in the relative incidence of aortic stenosis in these patients with unidentifiable gastrointestinal bleeding as compared to the 5 percent incidence for controls matched for age and sex.

Cody and co-workers[9] in a review of 610 Mayo Clinic patients with valvular heart disease found that 7 of 275 patients with aortic stenosis (2.6 percent) had idiopathic gastrointestinal bleeding while none of the 335 patients with other valvular diseases had idiopathic gastrointestinal bleeding. Several case reports subsequently appeared in the literature concerning the coexistence of aortic stenosis with recurrent idiopathic gastrointestinal bleeding.[10,11] Boss and Rosenbaum[3] reported a patient with aortic stenosis and recurrent idiopathic gastrointestinal bleeding in whom the right colon was found at autopsy to be the source of the bleeding. Microscopic examination showed distension of mucosal and submucosal veins and focal perivascular extravasations of blood. A similar case was presented by Treweeke[12] where the bleeding source was found to be in the ascending colon. In 1974 Galloway[4] reported the cases of three patients with aortic stenosis and gastrointestinal bleeding; not only was the site of bleeding shown to be the right side of the colon but the lesions were found by angiography to be submucosal vascular malformations.

Galdabini introduced the term colonic angiodysplasia to describe vascular lesions of the colon that histologically represent clusters of dilated vessels, mostly veins, in the mucosa and submucosa and which may become the source of low-grade chronic or intermittently massive rectal bleeding.[13,14]

The association of aortic stenosis and gastrointestinal bleeding secondary to such arteriovenous malformations was further supported by Gelfand.[5] He reported the cases of five patients with aortic stenosis who had multiple massive hemorrhages of the lower gastrointestinal tract and in whom conventional radiologic methods failed to identify the source of bleeding. Mesenteric angiography was required to show the vascular malformations. The lesions were found in the right part of the colon in four patients and in the jejunum in one. Colonoscopy did show the lesion in one of the patients.

Recently seven cases of patients with aortic stenosis and gastrointestinal bleeding have been reported, but in these patients the bleeding was upper gastrointestinal bleeding caused by gastric or duodenal arteriovenous malformations.[6,7] In the report by Weaver,[6] the six patients had aortic stenosis and either gastric or duodenal angiodysplasia as a cause of recurrent upper gastrointestinal bleeding. Endoscopy was of value in identifying the lesions in these patients. The authors emphasized that a high index of suspicion is needed to make the diagnosis since these lesions can be easily mistaken for trauma from the endoscope, nasogastric tube, suction artifact or gastritis.

The pathogenesis of the association of aortic stenosis and intestinal angiodysplasia remains unclear. Both congenital and acquired causes have been proposed. Others feel that association between aortic stenosis and these lesions is one of advanced age only. Speculation concerning the roles of chronic low cardiac output, vascular congestion, generalized arteriosclerosis and connective tissue degenerative disorders has been voiced. Of course, arteriovenous malformations of the gastrointestinal tract are not limited to patients with aortic stenosis,[15-19] suggesting that there may be multiple causes of gastrointestinal angiodysplasia. Recently, Love and co-workers reported two cases of calcific aortic stenosis and lower gastrointestinal bleeding where the bleeding stopped after aortic valve replacement.[20]

The occurrence of aortic stenosis and gastrointestinal bleeding secondary to arteriovenous malformations is uncommon, but it is also frequently difficult to diagnose as illustrated by the finding that in most of the reported cases there was a history of several hospital admissions, during each of which several units of blood were required before the correct diagnosis was made. One patient was reported to have had more than 50 admissions for the problem.[3]

The condition appears in patients of advanced age; in most of the reported cases the patients are in their 70's (53 to 90 years old). The bleeding is usually recurrent and often massive, as was illustrated by this case. Initial radiologic procedures will fail to show the site of the bleeding lesion because the arteriovenous malformation

does not create a mass effect. Except for a few cases in which it was possible to identify the lesion with colonoscopy, mesenteric angiography was almost always required for diagnosing lesions in the lower gastrointestinal tract. The utility of mesenteric angiography in establishing the diagnosis of gastrointestinal arteriovenous malformations was clearly demonstrated by Moore.[21] However, for the upper gastrointestinal lesions, endoscopy was shown to be of value.[6] In the presented case, although angiography suggested a site of active bleeding, the radiologic features did not suggest an arteriovenous malformation as the cause of the bleeding and, therefore, for upper gastrointestinal lesions careful endoscopy may be required for identification of such lesions. Surgical resection of the bleeding angiodysplastic lesions is curative. Potentially useful alternatives to a surgical procedure include endoscopic electrocoagulation[6,22,23] and endoscopic laser coagulation.[24] Weingart[22] and Weaver[6] reported the successful treatment of upper gastrointestinal angiodysplasia using endoscopic electrocoagulation. Rogers[23] reported five cases of colonic hemangiomas successfully treated by repeated colonic electrocoagulation.

The association between aortic stenosis and lower gastrointestinal bleeding secondary to angiodysplasia has now been well documented in the literature. That this association may be significant has been suggested by the two retrospective studies of Williams and Cody.[8,9] Reports of similar lesions occurring in cases of massive and recurrent *upper* gastrointestinal bleeding are now appearing in the literature, indicating a broader clinical and pathological spectrum for this syndrome and perhaps a greater frequency of occurrence than was previously recognized. Because most of the patients have severe, recurrent gastrointestinal bleeding, and because an operation is curative, a high index of suspicion, appropriate diagnostic procedures and definitive therapy may obviate the potential morbidity and mortality in this group of patients.

Summary

The association of aortic stenosis and colonic angiodysplasia in cases of recurrent lower gastrointestinal bleeding has been well documented in the literature. The case is presented of a patient with recurrent massive upper gastrointestinal bleeding in whom angiodysplasia of the stomach and aortic stenosis were found. This represents the eighth reported case of aortic stenosis and recurrent gastrointestinal bleeding from upper intestinal angiodysplasia, suggesting a broader clinical spectrum to the previously described association. The condition of aortic stenosis and gastrointestinal angiodysplasia primarily appears in patients of advanced age. The bleeding is usually recurrent and often massive. Angiography is usually required to identify intestinal lesions; however, endoscopy can be of value in identifying gastric lesions. Because specific therapy may be available, invasive diagnostic procedures are indicated in patients with aortic stenosis and recurrent unexplained gastrointestinal bleeding.

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Superior Vena Cava Syndrome in Children

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THE SUPERIOR VENA CAVA SYNDROME is an uncommon manifestation of malignant neoplastic disease in children. Only 9 cases were found among 607 children with solid tumors seen between 1956 and 1962 at Children's Hospital Medical Center in Boston.[1] Although malignant lymphomas are the most common cause in children, other neoplasms may be associated with this syndrome. This report describes our recent experience with five children admitted to Primary Children's Medical Center between October 1978 and October 1979 with the superior vena cava syndrome. Their management is discussed and the literature reviewed.

Reports of Cases

CASE 1. A 7-year-old white boy was admitted to PCMC in October 1978 with a two-week history of cough, fever, fatigue and shortness of breath. A physical examination showed that the patient was acutely ill and in moderate respiratory distress. His blood pressure was 108/68 mg of mercury, pulse 150 beats per minute and respirations 60 per minute. Temperature was 37.8°C (100°F). His face was plethoric and his neck veins were distended and filled from below. He had moderately enlarged cervical and axillary lymph nodes bilaterally. The breath sounds were decreased and there was dullness to percussion over the entire right side of the chest. The liver was palpable 3 to 4 cm beneath the right costal margin and the superficial veins over the upper abdomen and anterior thorax were dilated. The spleen was not enlarged.

Laboratory results were as follows: hemoglobin 15 grams per dl, hematocrit 44 percent, platelet count 433,000 per cu mm and leukocyte count 13,800 per cu mm, with 63 percent neutrophils and 31 percent mature lymphocytes. An x-ray study of the chest showed opacification of the entire right hemithorax and large superior mediastinal mass. There was also atelectasis of the left lower lobe and a small pleural effusion on the left side. A right-sided thoracentesis yielded 1,500 ml of opaque yellow fluid, which contained numerous immature lymphoid cells. An aspirated bone marrow specimen contained 71 percent lymphoblasts, establishing the diagnosis of acute lymphoblastic leukemia.

The boy was treated with orally given prednisone daily and intravenously given vincristine weekly. A series of intramuscular injections of l-asparaginase was administered as well. Five days after starting chemotherapy a roentgenogram of the chest showed a striking reduction in the size of the mediastinal mass (Figure 1). The patient improved rapidly and progressively and was discharged on the tenth hospital day. He achieved complete remission of his disease and has remained in continuous complete remission to date while receiving multiagent chemotherapy.

CASE 2. This 6-year-old white boy was admitted to PCMC in October 1978 with a one-month history of facial puffiness and a two-day history of enlarged neck veins with cyanosis of the lips and ears. A physical examination showed a well-nourished, well-developed child in mild respiratory distress and with orthopnea. His blood pressure was 110/70 mm of mercury, pulse 100 per minute, respirations 30 per minute and temperature 36.3°C (97.3°F). His face and neck were darkly plethoric and edematous. His neck veins were distended and filled from below. There was a prominent venous pattern over his anterior chest. His chest was clear and an examination of his heart showed no abnormalities. His liver was palpable 1.5 cm beneath the right costal margin. There was no splenomegaly or lymphadenopathy.

Laboratory evaluation included the following: hemoglobin 12 grams per dl, hematocrit 41 percent, platelet count 356,000 per cu mm and leu-

ABBREVIATIONS USED IN TEXT

IVP = intravenous pyelogram
PCMC = Primary Children's Medical Center
SVCS = superior vena cava syndrome

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Figure 1.—(Case 1) Comparison of x-ray film of the chest after thoracentesis **(left)** with film taken five days after initiation of multiagent chemotherapy **(right)**, showing a dramatic decrease in mediastinal mass. Bilateral pleural effusions present.

Figure 2.—(Case 2) Widening of the superior mediastinum, with interstitial parenchymal densities representing pulmonary venous obstruction.

kocyte count 8,100 per cu mm, with 73 percent neutrophils, 11 percent mature lymphocytes and 9 percent lymphoblasts. An x-ray study of the chest showed a diffuse fusiform widening of the superior mediastinum, with an extensive interstitial pulmonary pattern extending out from the hilum into the peripheral lung fields (Figure 2). A superior vena cavagram showed obstruction to venous blood returning to the heart, with extensive collateral venous circulation. Findings of a bone marrow aspiration were unremarkable. Lymph node biopsy specimens obtained by mediastinoscopy and from the scalene fat pad showed benign fibrotic nodes. A second bone marrow aspiration and biopsy were again nondiagnostic. Following mediastinoscopy the patient showed some clinical improvement and was discharged without a specific diagnosis.

He was readmitted four weeks later with recurrence of the original signs and symptoms. An exploratory thoracotomy of the right side was done, at which time extensive fibrosis of the mediastinum was found. One of three biopsy specimens obtained at the time of the operation, however, showed a malignant tumor consisting of a mixture of epithelial cells and immature lymphoid cells. Electron microscopy showed epithelial cells with desmosomes and numerous tonofilaments admixed with primitive lymphoid cells. A diagnosis of thymoma with malignant lymphoid elements was made. The other two biopsy specimens showed only fibrosis.

The patient was treated with pulses of cyclophosphamide, adriamycin, vincristine and prednisone every three to four weeks. He improved clinically and roentgenographically within a few days. Four months later evidence of superior vena cava syndrome recurred. A repeat aspiration of bone marrow showed no abnormalities. The patient's chemotherapy regimen was changed to a combination of methotrexate and 1-asparaginase given every two weeks. Complete remission was again achieved. This regimen has been maintained to date without evidence of disease.

CASE 3. A 3-year-old white girl was admitted to PCMC in May 1979 with a two-week history of cough and a one-day history of fever. On physical

examination the girl appeared well-nourished and well-developed but in mild respiratory distress. Her blood pressure was 110/70 mm of mercury, pulse 120 per minute, respirations 36 per minute and temperature 37.0°C (98.6°F). The neck veins were distended and filled from below. The breath sounds were decreased over the entire right side of the chest. The liver was palpable 6 cm beneath the right costal margin, and the spleen tip was palpable. There was no lymphadenopathy.

Laboratory results were as follows: hemoglobin 12.4 grams per dl, hematocrit 39.2 percent, platelet count 505,000 per cu mm and leukocyte count 14,800 per cu mm, with 52 percent neutrophils and 42 percent mature lymphocytes. An x-ray study of the chest showed extensive opacification of the right hemithorax, which on ultrasound testing proved to be due to a solid mass. Results of a bone marrow aspiration were within normal limits. A right-sided thoracotomy was done and histological studies of the frozen section detected what appeared to be a poorly differentiated, small cell, malignant neoplasm consistent with a neuroblastoma. The tumor was resected but with some residual disease left behind. Permanent histological sections by light and electron microscopy showed that the tumor was a poorly differentiated diffuse lymphocytic lymphoma. Further workup to define the extent of the disease, including bone marrow biopsy, liver-spleen scan, intravenous pyelogram (IVP), metastatic series and lumbar puncture, gave negative results.

The patient was given pulses of cyclophosphamide, adriamycin, vincristine and prednisone every three weeks. On that regimen the disease has remained in continuous complete remission to the present.

CASE 4. A 2-year-old white girl was admitted to PCMC in September 1979 with a one and a half week history of facial swelling, lethargy and wheezing. Results of a physical examination showed the child to be well-nourished, well-developed and in no acute distress. Her blood pressure was 92/58 mm of mercury, pulse 100 per minute, respirations 32 per minute and temperature 37.6°C (99.7°F). Her face was edematous and cyanotic, and her conjunctivae were injected. Her neck veins were distended and filled from below. Her chest was clear and there was no lymphadenopathy or hepatosplenomegaly.

Laboratory studies gave the following values: Hemoglobin 11.8 grams per dl, hematocrit 36.2 percent, platelet count 620,000 per cu mm and leukocyte count 9,200 per cu mm, with 32 percent neutrophils and 57 percent mature lymphocytes. An x-ray film of the chest showed a large anterior-superior mediastinal mass (Figure 3). Results of a bone marrow aspiration were within normal limits. A biopsy specimen obtained by mediastinoscopy was studied by light and electron microscopy and a diagnosis of a yolk sac tumor was made. Alpha-fetoprotein was 32,780 ng per ml. Workup to define the extent of the disease, including IVP, pelvic and abdominal ultrasound testing, liver-spleen scan, bone scan, metastatic series and bone marrow aspiration, was negative.

Figure 3.—(Case 4) Primary mediastinal yolk sac tumor associated with superior vena cava syndrome.

An attempt to excise the tumor resulted in gross removal with a small amount of residual tumor left behind in the chest. A regimen involving cycles of multi-agent chemotherapy (actinomycin-D, adriamycin, vincristine and cyclophosphamide) was begun and radiation therapy was administered to the tumor bed. She is currently asymptomatic with unremarkable findings on physical examination.

CASE 5. A 17-month-old white boy was admitted to PCMC in October 1979 with a two-week history of an enlarging mass at the site of a burn that was healing on the left forearm and a one-week history of cough and progressive tachypnea. The infant appeared both acutely and chronically ill. His blood pressure was 80/50 mm of mercury, pulse 128 per minute, respirations 36 per minute and temperature 37.6°C (99.7°F). He seemed anxious and irritable and had neck and facial edema. His neck veins were distended and filled from below. His chest was clear and findings of an examination of his heart were unremarkable. The

liver was palpable 2 cm beneath the right costal margin and there was no splenomegaly. He had a 3-cm soft, nontender left-sided axillary lymph node. There was a 4×5 cm erythematous, firm mass on the left forearm medial to the elbow.

Laboratory evaluation gave the following results: Hemoglobin 9.3 grams per dl, hematocrit 31.3 percent, platelet count 300,000 per cu mm and leukocyte count 8,100 per cu mm, with 23 percent neutrophils and 75 percent mature lymphocytes. An x-ray film of the chest showed a prominent superior mediastinum and pulmonary venous congestion. Findings of a bone marrow aspiration were within normal limits. A biopsy specimen of the mass on the infant's left elbow was obtained while he was under local anesthesia. The diagnosis of histiocytic lymphoma was made using light and electron microscopy. Results of a liver-spleen scan, bone scan and metastatic series were within normal limits.

The patient was treated with combination chemotherapy (cyclophosphamide, adriamycin, vincristine and prednisone) and within 48 hours showed symptomatic improvement. His first follow-up chest x-ray film two weeks after the initiation of therapy showed striking improvement.

Discussion

The superior vena cava syndrome (SVCS) results from an obstruction of venous drainage in the superior mediastinum. The obstruction is generally due to extrinsic compression of these thin-walled, low-pressure vessels, which are fixed and surrounded by firmer structures.[2] The resultant increase in venous pressure causes dilation of the veins beyond the obstruction, the development of collateral venous drainage, edema with plethora or cyanosis of the face and neck and, sometimes, symptoms involving the central nervous system. A variant, referred to as the superior mediastinal syndrome, has the additional feature of respiratory symptoms such as cough, wheezing or respiratory distress due to compression of the trachea or bronchi.[1]

This report illustrates the spectrum of clinical manifestations and associated findings in children with SVCS. The duration of symptoms before diagnosis was usually about two weeks. The physical findings at diagnosis varied from isolated neck vein distension to the full syndrome of neck vein distension, edema and plethora or cyanosis of the face, and the presence of collateral venous circulation. Respiratory symptoms or physical findings were prominent presenting features in all of our patients. They were frequently one of the major complaints for which medical attention was initially sought. Four of our five patients presented with either cough or wheezing, and four had evidence of respiratory distress with tachypnea, dyspnea or orthopnea at diagnosis.

In the past, syphilitic aneurysms and tuberculous mediastinitis were frequent causes of SVCS,[3] but today more than 95 percent of the cases are secondary to malignant neoplasms. In adults, bronchogenic carcinoma accounts for about 75 percent of the cases and lymphomas account for most of the remainder.[4] Most children with SVCS have lymphoproliferative disorders as did three of our patients. Other malignant neoplasms, such as neuroblastoma[1,5] and Ewing's sarcoma,[6] have been reported occasionally, and we now report for the first time in children an association with a primary yolk sac tumor and a thymoma. Thymomas causing SVCS have been noted in adults.[8] Other less common, nonneoplastic causes include trauma, goiters, sarcoidosis and fungal infections. The SVCS can occur as a late complication of the Mustard operation for transposition of the great vessels.[9] Rare cases of idiopathic mediastinal fibrosis with superior vena cava obstruction have been reported.[10] Patient 2 had pronounced fibrosis of the mediastinum in association with a neoplasm that under the light and electron microscope was diagnosed as a thymoma with immature lymphoid elements. Lymphoblasts were present in the peripheral blood but results of bone marrow examinations were repeatedly normal. One similar case has been reported previously.[7] This case will be described in detail in a separate paper.

With the increasing use of central venous catheters for monitoring and hyperalimentation, the SVCS is now being reported as a complication of those procedures.[11] Thrombosis is the mechanism for the obstruction of venous drainage under these circumstances.

The recognition of the potential or actual emergency nature of the syndrome is important and has resulted in the recommendation from some to institute therapy before obtaining a histological diagnosis.[12,13] Undoubtedly there are individual situations where such a recommendation would be warranted. Nonetheless, the importance of obtaining a definitive histological diagnosis needs to be stressed. That information could possibly influence how the SVCS is treated, and certainly it is important as far as future therapy and prog-

nosis are concerned. Because lymphoma, the most common cause of the SVCS syndrome in children, has such a high frequency of marrow involvement[14] and leukemic transformation,[15] a bone marrow aspiration should be one of the first diagnostic procedures done. It may yield a specific diagnosis and spare the patient unnecessary operations. Case 1 is an illustration of that point. A histological diagnosis often can be obtained from a limited surgical procedure, such as a peripheral node biopsy or mediastinoscopy, as occurred in two of our five patients (cases 4 and 5). If a thoracotomy is needed to obtain a specimen for histological diagnosis, an adequate tissue sample can usually be obtained through a small parasternal incision. The procedure of choice, if one is needed, to make a histological diagnosis should be decided on an individual basis, depending on the physical findings and the clinical condition of each patient.

The initial goal in the management of the SVCS is the *prompt* relief of the venous obstruction and respiratory symptoms. Radiation has been considered the primary therapeutic modality.[4] That recommendation comes largely from the adult literature where there have been studies that showed no additive therapeutic effect of chemotherapy.[16] Also, most of those patients had bronchogenic carcinoma, where radiation probably offers the best chance of achieving that initial goal. Radiation also is often rapidly effective in the treatment of lymphomas. In children in whom non-Hodgkin's lymphomas account for most of the cases of SVCS, combination chemotherapy may be as effective as radiation therapy in achieving a prompt response. Patients 1, 2 and 5 were treated with multiagent chemotherapy only, and they all showed dramatic clinical improvement within 48 to 72 hours. We suggest that multiagent chemotherapy be seriously considered as the primary therapy of the SVCS in children who have documented lymphoproliferative disease.

Surgical procedures generally are not indicated for the treatment of SVCS. The most common neoplasms associated with the syndrome, bronchogenic carcinoma and lymphoma, usually cannot be completely excised and are better treated with other modalities. Operations, however, do play an important role in the treatment of thymomas, which have been reported associated with SVCS in adults.[8] A surgical procedure may also be indicated in the initial therapy of children with less common neoplasms that cause SVCS, such as Ewing's sarcoma,[6] neuroblastoma[1,5] and yolk sac tumor. Management decisions for children with cancer should result from the combined input of a multidisciplinary pediatric team that includes surgeons, radiation oncologists, medical oncologists and pathologists.

Although the SVCS represents a potentially life-threatening complication of neoplastic disease, our experience indicates that a prompt and aggressive approach to diagnosis and management will generally yield a favorable response. The long-term prognosis for patients with SVCS, therefore, should depend on the specific histological findings and the extent of disease at diagnosis. Recent reports have shown an improved prognosis for children with lymphomas occurring in the mediastinum.[17]

Summary

This paper presents our recent experience with five children with neoplastic disease who presented with the SVCS. It reports for the first time an association of the SVCS in children with a primary yolk sac tumor and a thymoma. The value of a specific histological diagnosis and methods for obtaining it are emphasized. The causes, pathophysiology, clinical manifestations and management of the SVCS in children are discussed.

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
DKA = diabetic ketoacidosis

Adult Respiratory Distress Syndrome Complicating Diabetic Ketoacidosis

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THE MOST COMMON associated causes of noncardiogenic pulmonary edema are sepsis, trauma, aspiration, drug overdose, shock, extensive pneumonia and acute pancreatitis.[1,2] We report here an unusual case in which the adult respiratory distress syndrome (ARDS) developed in association with diabetic ketoacidosis (DKA) alone. We established the noncardiogenic origin of the pulmonary edema on the basis of a high protein concentration in airway edema fluid and low pulmonary artery wedge pressures. We excluded other clinical disorders that have been associated with ARDS on the basis of the initial workup, clinical course and postmortem examination.

Report of a Case

A 49-year-old woman had had adult-onset diabetes mellitus for five years and was being treated with chlorpropamide, 250 mg twice a day. For two days before her admission, nausea, vomiting and weakness had occurred. There was no history of alcohol or drug abuse. Physical examination showed Kussmaul-type respirations (30 per minute), a pulse rate of 120 beats per minute, and blood pressure of 105/80 mm of mercury supine and 80/50 mm of mercury sitting. Her body temperature was 35°C (95°F). On neurologic examination no focal abnormalities were noted. Her mental status alternated between mild agitation and slight drowsiness. An examination of the chest showed no abnormalities and only decreased bowel sounds were noted on examination of the abdomen. Findings on the rest of the admitting physical examination were within normal limits. Laboratory data included the following: serum sodium 127, potassium 4.7, chloride 100 and bicarbonate 4 mEq per liter; blood glucose 652 mg per dl; serum ketones positive to a dilution of 1:16. Arterial blood gases while breathing room air, corrected for body temperature, were pH 6.9, and oxygen pressure (P_{O_2}) 119 and carbon dioxide pressure (P_{CO_2}) 12 mm of mercury. The calculated alveolar-arterial oxygen gradient was 16 mm of mercury (normal less than 20). The hematocrit was 52 percent and the leukocyte count was 25,600 per cu mm, with a differential of 72 neutrophils, 2 bands, 3 metamyelocytes, 13 lymphocytes and 10 monocytes. Prothrombin time, partial thromboplastin time, the platelet count, and liver function tests were within normal limits. An electrocardiogram showed only sinus tachycardia. An x-ray study of the chest (upright anterior-posterior) showed no abnormalities (Figure 1). On analysis of urine only glycosuria and ketonuria were noted. Specimens of urine and blood were sent for culture.

The patient was treated with two ampules of sodium bicarbonate (44 mEq of sodium each), continuous intravenously given insulin, and four liters of intravenously given crystalloid fluids over the next six hours. Clinically she was responding well to therapy as the metabolic acidosis gradually improved. However, eight hours after admission she became dyspneic and agitated.

On physical examination there were rhonchi and rales noted over both lung fields. An x-ray film of the chest showed alveolar infiltrates predominantly in the right lower lobe and the left upper lung field. Arterial blood gases while breathing room air showed a pH of 7.24, P_{O_2} of 60 and P_{CO_2} of 34 mm of mercury. No expectorated sputum was available for examination. The blood glucose level was 214 mg per dl, electrolytes were normal except for a bicarbonate value of 12 mEq per liter. The hematocrit was 47 percent and the leukocyte count had fallen to 4,800 per cu mm. Results of repeat platelet count and coagulation tests were normal. A serum amylase determination, the specimen drawn on admission, was

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reported to be 1,050 IU per liter (normal less than 200). Two more blood specimens for culture were drawn, and a spinal tap showed normal opening pressure, no cells, negative Gram stain, and normal cerebrospinal fluid glucose and protein levels.

The patient's status continued to deteriorate and two hours later endotracheal intubation and mechanical ventilation were required. On fraction of inspired oxygen (FIO_2) of 1.0, arterial blood gases showed a pH of 7.32, Pco_2 of 35 and Po_2 of 50 mm of mercury. High pressure (50 cm of water) was required to deliver 900 ml tidal volume. On a portable anteroposterior chest film, extensive bilateral alveolar infiltrates were seen (Figure 2). A pulmonary artery line was inserted; there was a normal pulmonary artery wedge pressure of 11 mm of mercury and a pulmonary artery pressure of 38/12 mm of mercury. Cardiac output by thermodilution was 4.6 liters per minute. There was frothy, slightly sanguinous fluid foaming out of the patient's endotracheal tube. Samples of this fluid were taken for protein measurements. A serum specimen for protein measurement was drawn at the same time. Microscopic examination of the airway fluid showed no leukocytes, no bacteria, a moderate number of red blood cells (hematocrit less than 1 percent) and a few alveolar macrophages.

The working clinical diagnosis was acute pancreatitis with possibile sepsis and respiratory failure secondary to ARDS. Therapy with broad spectrum antibiotics was begun and 1 gram of methylprednisolone was given intravenously. The patient did not respond well to 5 cm of positive end-expiratory pressure as the cardiac output fell to 3 liters per minute. Three hours later she died with hypotension and severe hypoxemia. Permission for an autopsy was granted.

On postmortem examination the lungs were heavy and edematous (right lung 800 grams, left lung 1,200 grams). Microscopic study showed extensive interstitial and alveolar edema with a moderate number of inflammatory cells, mostly neutrophils. Gram stains of the tissue were negative for bacteria, acid fact bacilli or fungi. All the premortem and postmortem blood cultures remained negative for four weeks. Cultures of spinal fluid and lung tissue were negative. No source of infection was found at autopsy. Examination of the central nervous system, heart and abdomen showed no abnormalities. There was no gross or microscopic evidence of pancreatitis.

The results of protein measurements on the airway edema fluid and the plasma in this case are presented in Table 1. Fein and co-workers reported in their series of 21 patients with ARDS and normal pulmonary capillary wedge pressure measurements that the mean airway edema fluid

TABLE 1.—*Edema Fluid Protein Measurement*

	Edema Fluid (grams per dl)	*Plasma (grams per dl)*	*Ratio (edema/plasma)*
Total protein	3.60	4.36	.83
Albumin	2.28	2.40	.95

Figure 1.—Erect anteroposterior x-ray study of the chest made on admission.

Figure 2.—Erect anteroposterior x-ray study of the chest made ten hours after admission.

to plasma protein ratio exceeded 0.6.[3] In our patient the total protein content in airway fluid was very high, equal to 0.83 of the plasma total protein value. This correlates with a severe permeability of the alveolar-capillary membrane and is compatible with her rapidly fatal clinical course.

Discussion

The clinical disorders usually associated with ARDS were systematically eliminated in reviewing this patient's case.[1,2] Sepsis was excluded by the multiple negative blood cultures and the lack of any focus of infection on postmortem examination. Acute pancreatitis was excluded by the autopsy. High levels of serum amylase have been reported in DKA without associated acute pancreatitis.[4] There was also no evidence of aspiration before this patient came to the hospital. An x-ray study of the chest was normal (Figure 1), as was alveolar-arterial oxygen gradient on admission. Subsequently, she was under constant observation in the intensive care unit. A neurogenic cause of the pulmonary edema was ruled out by the normal cerebrospinal fluid pressures, normal spinal fluid study results and lack of any central nervous system abnormalities at autopsy. There was no history or physical findings suggestive of drug overdose, and the metabolic acidosis resolved appropriately with therapy of the DKA. Finally, there was no evidence of disseminated intravascular coagulation.

Powner and associates did report in 1975 the case of a 24-year-old patient with a possible noncardiogenic pulmonary edema that developed in association with DKA alone.[5] There were no measurements, however, of pulmonary artery wedge pressure until the patient was extubated and clinically improved. Therefore, cardiogenic pulmonary edema could not be completely ruled out. The patient survived so there was no postmortem examination, and the authors did not measure airway edema fluid protein content. Recently, Sprung and co-workers reported the cases of two patients with DKA in whom pulmonary edema developed with low pulmonary capillary wedge pressure.[6] Both of their patients died, but postmortem examinations were not done.

Our case is the first one reported of ARDS with DKA alone, with measurements of pulmonary capillary wedge pressures, airway edema fluid/plasma protein ratios and postmortem confirmation that there was no occult cause of the acute lung injury other than DKA.

We can only speculate regarding the mechanism or mechanisms of our patient's acute respiratory failure. Diabetic patients have been shown to have increased permeability of capillary membranes.[7] Powner suggested that perhaps this baseline abnormal capillary permeability could be increased when there is severe acidosis in DKA.[5] Our patient's acidosis (pH 6.9) was severe when she was admitted. However, many patients are very acidotic when they present with DKA so there must be some additional factor or factors that produce acute lung injury. In our patient, the dramatic fall in the circulating leukocyte count from admission to the onset of her pulmonary edema was out of proportion to the mild hemodilution effect of intravenous crystalloid replacement. It is possible that the severe acidosis coupled with decreased perfusion from hypovolemia resulted in complement activation and intrapulmonary sequestration of leukocytes with secondary lung injury.[8,9] The most recent experimental evidence suggests that leukocytes are the critical mediators of acute lung injury in two different experimental models of permeability pulmonary edema.[10,11]

Summary

Within eight hours of hospital admission of a 49-year-old woman for severe diabetic ketoacidosis, rapidly fatal pulmonary edema developed with the clinical features of the adult respiratory distress syndrome. Clinical disorders usually associated with acute lung injury were excluded. Severe diabetic ketoacidosis can be added to the list of clinical disorders associated with ARDS.

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Isolated Right Upper Lobe Pulmonary Edema

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ATYPICAL ACCUMULATION of fluid within the lung may produce unilateral or dominantly lobar pulmonary edema.[1] Unilateral pulmonary edema has been attributed to numerous causes including rapid evacuation of a pneumothorax, systemic-to-pulmonary artery shunt for cyanotic congenital heart disease, rapid thoracocentesis and renal transplantation.[2-7] Pulmonary edema localized to one lobe is exceedingly rare and is usually present in the right upper lobe.[8] We present two cases of lobar edema and possible mechanisms for the localization of the fluid.

Reports of Cases

CASE 1. A 67-year-old woman with adult-onset diabetes who had had one previous episode of myocardial infarction was admitted to a local hospital because of an anterior myocardial infarction. A week after discharge she returned because of increasing shortness of breath and epigastric pain. On readmission, a physical examination of the patient disclosed moderate pedal edema and rales at the lung bases; no heart murmurs were heard. Laboratory values for creatinine phosphokinase (CPK), serum aspartate aminotransferase and lactic dehydrogenase (LDH) were within normal limits. Findings on a chest roentgenogram and a perfusion lung scan showed no abnormalities. Her electrocardiogram was unchanged from previous studies. A week later, however, a repeat x-ray study of the chest showed right upper lobe consolidation, and the patient was transferred to our institution for further evaluation. On admission, she appeared acutely ill. Her blood pressure was 170 mm of mercury diastolic, pulse rate was 120 and respiratory rate 36 per minute; temperature was 37.5°C (99.5°F). Jugular vein distension to 16 cm and pronounced pedal edema were present. A soft S_1, a loud P_2, and an S_3 gallop were heard. A grade 3/6 holosystolic murmur was audible at the apex of the heart and radiated to the left axilla. The lung fields demonstrated dullness at both bases and rales up to scapulae. Arterial blood gases exhibited a partial pressure of oxygen (Pa_{O_2}) of 95 mm of mercury, a slightly low partial pressure of carbon dioxide (Pa_{CO_2}) and a serum pH of 7.39.

Laboratory values for serum bicarbonate, serum electrolytes, hemoglobin and hematocrit were all within normal limits. Blood urea nitrogen (BUN) was 56 mg per dl and creatinine 2.3 mg per dl. A leukocyte count was 14,200 per cu mm, with a normal differential count.

A roentgenogram of the chest showed patchy consolidation in the right upper lobe and small bilateral pleural effusions (Figure 1). A tentative diagnosis of pneumonia was made, although pulmonary hemorrhage, infarction and contusion were considered in the radiographic differential diagnosis. Microscopic examination of sputum and transtracheal aspirate specimens detected no polymorphonuclear leukocytes or organisms. Pleural fluid, obtained by thoracocentesis, was a transudate with no organisms. Cultures of sputum, transtracheal aspirate and pleural fluid grew no organisms. A Swan-Ganz thermodilution catheter was positioned in the right pulmonary artery and subsequently wedged in the right upper lobe consolidation. The right atrial pressure was 17 mm of mercury and pulmonary artery pressure 78/40 mm of mercury (mean 59 mm of mercury). Pulmonary capillary wedge pressure was 44, with a "V" wave of 65 mm of mercury. Cardiac output was 3.1 liters per minute, with an arteriovenous oxygen difference of 9.9 ml per dl and a systemic vascular resistance of 2,323 dyne•sec•cm^{-5}. CPK and LDH isoenzyme values suggested acute myocardial in-

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CPK = creatinine phosphokinase
LDH = lactic dehydrogenase
Pa_{CO_2} = partial pressure of carbon dioxide (arterial)
Pa_{O_2} = partial pressure of oxygen (arterial)

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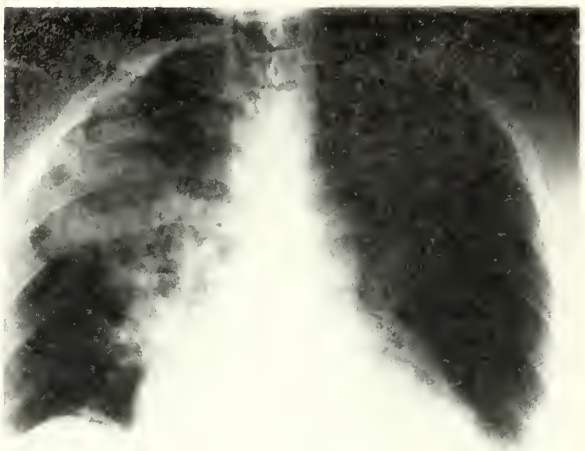

Figure 1.—(Case 1) Frontal portable roentgenogram of the chest shows dense, right upper lobe consolidation. The remainder of the lung fields is essentially clear.

farction. A clinical diagnosis was made of papillary muscle dysfunction leading to acute mitral regurgitation.

The patient was treated by afterload reduction with nitroprusside and showed improvement in cardiac output and a pronounced decrease in pulmonary capillary wedge pressure. The right upper lobe consolidation cleared in 24 hours, indicating the correct diagnosis of lobar pulmonary edema. Subsequent cardiac catheterization showed moderate to substantial mitral regurgitation, apico-inferior myocardial hypokinesis and diffuse coronary artery disease involving three vessels.

CASE 2. A 26-year-old woman was admitted to a local hospital for hypertension and slow thought processes. Five years before, hemodialysis had been initiated for end-stage renal failure caused by chronic glomerulonephritis and hypertension. She had had a successful cadaver renal transplantation two years later. Her maintenance medications included 75 mg per day of azathioprine and 30 mg per day of prednisone. Two weeks before admission she began to gain weight and peripheral edema developed. When admitted to the hospital, she had tenderness over the site of her renal graft and elevated BUN and serum creatinine levels. A diagnosis of allograft rejection was made and the patient was treated with 60 mg per day of prednisone and a continuance of 75 mg of azathioprine per day. She did not improve and after a week was transferred to our institution for placement of a vascular shunt for maintenance hemodialysis.

At the time of transfer, her mentation was still sluggish, but she had no chest pain, cough or dyspnea. She was 15 lb (6.8 kg) over her usual weight, peripheral edema was pronounced, and blood pressure was 190/120 mm of mercury. The

A

B

Figure 2.—(Case 2) **A**, Frontal roentgenogram of the chest at the time the patient was transferred shows patchy consolidation in most of the right upper lobe. The remainder of the lung fields is clear and the pulmonary vessels are of normal caliber. Cardiomegaly is visible. **B**, A roentgenogram done three days later shows the right upper lobe consolidation has completely resolved. The pulmonary vessels and cardiac size are unchanged.

lung fields were clear to auscultation. Cardiac auscultation showed that S_1 and S_2 were normal; a soft systolic murmur and an S_4 but no S_3 gallop were audible. BUN was 204, creatinine 12.7 and serum albumin 3.0 mg per dl. A leukocyte count was 6,400 per cu mm; Pa_{O_2} was 54 and Pa_{CO_2} was 38 mm of mercury; pH was 7.37.

An earlier roentgenogram of the chest had shown moderate cardiomegaly with clear lung fields; however, another roentgenogram, made when the patient arrived at our institution, showed fluffy air space consolidation involving only the right upper lobe (Figure 2A). Cardiomegaly and minimally blunted costophrenic angles were also visible. The tentative clinical and radiographic diagnosis was pneumonia or pulmonary hemorrhage.

Because sputum cultures grew no pathogenic organism and tuberculin and fungal skin tests had been negative, antibiotic drugs were not given. Fiberoptic bronchoscopy was planned for the day following the x-ray study of the chest. In the interim, the patient underwent hemodialysis and lost 2.2 kg. The Pa_{O_2} rose to 74 mm of mercury and pH increased to 7.43. Another roentgenogram showed partial clearing of the right upper lobe consolidation, and bronchoscopy was deferred. On the third day after admission, the patient again underwent hemodialysis and lost an additional 2.2 kg. A chest roentgenogram showed complete clearing of the right upper lobe consolidation (Figure 2B), indicating the correct diagnosis of lobar pulmonary edema.

Discussion

The distribution of pulmonary edema is determined by the hydrostatic forces across the pulmonary microcirculation and by the permeability of the pulmonary capillary bed. Edema fluid usually accumulates at the lung bases. Unilateral pulmonary edema can occur when local forces predominate or when the pulmonary vasculature or pulmonary parenchyma is abnormal (Table 1).[9]

Acute consolidation of the right upper lobe is usually due to pneumonia or obstruction of the lobar bronchus. Occasionally, bleeding in the lung can produce acute lobar consolidation. Pulmonary edema limited to the right upper lobe is rare.[8]

In our first patient, right upper lobe consolidation occurred shortly after an acute myocardial infarction with papillary muscle dysfunction and severe acute mitral regurgitation. A retrograde flow of blood due to the regurgitation can be directed across the left atrium toward the orifices of the right upper lobe pulmonary veins.[10] We think that this backflow, or backpressure, into the right upper lobe pulmonary veins could have resulted in a focal increase in pulmonary venous pressure. Pulmonary wedge pressure obtained in the right upper lobe at the time of the pulmonary consolidation was 44 mm of mercury with a "V" wave of 65 mm of mercury, reflecting mitral incompetence. Therapy by afterload reduction resulted in the rapid clearing of the consolidation. In a patient with acute mitral regurgitation, the presence of right upper lobe consolidation may represent focal pulmonary edema resulting from local elevation in pulmonary venous pressure. The radiographic features of left heart failure should be carefully sought; they include septal lines, an increase in the caliber of the upper lobe vessels and peribronchial cuffing.

TABLE 1.—*Differential Diagnosis of Unilateral Pulmonary Edema*

Gravity
Rapid evacuation of a pneumothorax
Rapid thoracocentesis
Aspiration of gastric acid and other materials
Contralateral chronic obstructive pulmonary disease associated with left heart failure
Contralateral obliterative bronchiolitis associated with left heart failure
Acute left heart failure and associated pneumothorax (protective effect)
Systemic-to-pulmonary artery shunt for cyanotic congenital heart disease
Bronchial obstruction (drowned lung)
Renal transplantation

The second case is less easily explained by focal hemodynamic effects. Although the patient did have a soft systolic murmur, she had no definitive evidence of a myocardial infarction or mitral regurgitation. Pulmonary vascular pressures were not measured. Local abnormal capillary permeability may have been present. The patient was in renal failure and "uremic pneumonitis" may have produced focal consolidation. This poorly understood condition may be a form of focal pulmonary edema.

Pulmonary symptoms, especially in an immunosuppressed patient, are often not helpful in distinguishing pnuemonia from edema.[11] The possibility of an infectious cause for the lobar consolidation was initially considered in both patients, but rapid clearing occurred without anti-

microbial therapy. Failure to consider edema may lead to unnecessary investigation and important delay in initiating therapy.

Summary

Two cases of right upper lobe pulmonary edema with focal lung consolidation are presented. In both patients, the initial clinical and radiographic differential diagnosis was pneumonia, infarction or pulmonary hemorrhage. In one of the two patients, acute mitral regurgitation from papillary muscle dysfunction was probably responsible for the focal pulmonary edema. In the other patient, "uremic pneumonitis" may have caused the focal consolidation. In both patients the consolidation cleared rapidly without antimicrobial therapy.

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Locating a Parathyroid Adenoma by Ultrasonography and Aspiration Biopsy Cytology

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ULTRASONOGRAPHY is being used to show the precise location of parathyroid tumors before operation in patients with primary hyperparathyroidism.[1-3] One of the problems with this technique is that ultrasonography cannot distinguish between a parathyroid tumor and other lesions, such as thyroid nodules and lymph nodes, situated in the same locations.[4] False-positive diagnoses are, therefore, common. False-negative diagnoses may also occur because of the inability to localize some small parathyroid tumors. This report concerns a patient with persistent hypercalcemia. His case presented numerous diagnostic difficulties, and eventually it was documented that the patient had at least six parathyroid glands, two being adenomatous. An elusive second adenoma was eventually localized by ultrasonography and confirmed by aspiration biopsy cytology. To our knowledge this is the first report of locating a nonpalpable parathyroid adenoma by such a combination of procedures. Because hyperparathyroidism is a common disorder, occurring in 1 in 700 persons and usually a result of a solitary parathyroid adenoma, the combined use of ultrasonography and aspiration biopsy cytology may prove to be valuable in selected patients with hyperparathyroidism.[5-7]

Report of a Case

A 70-year-old man had a radical cystectomy and pelvic node dissection with ileal loop diversion five years previously for a grade 2 to 3 transitional cell carcinoma of the bladder with squamous metaplasia. None of 13 nodes were involved. At that time, his calcium level measured 11.1 mg per dl and phosphorus 2.2 mg per dl. A year later he was without evidence of recurrent tumor. The diagnosis of primary hyperparathyroidism was considered, however, because of persistent hypercalcemia in a hypertensive patient with symptoms of polydipsia and constipation. The

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patient stated that he did not take excessive amounts of milk products, antacids or vitamins. Pertinent laboratory data included these findings: calcium 10.6 to 11.1 mg per dl (normal 8.5 to 10.5), phosphorus 2.1 to 1.9 mg per dl, magnesium 1.7 mEq per liter, parathyroid hormone (PTH) 175 μIEq per ml (normal less than 90, Nichols Institute, San Pedro, California), chloride 108 mEq per liter, alkaline phosphatase 120 mU per ml (normal 30 to 115), percent tubular resorption of phosphate 69.8, hemoglobulin 15.9 grams per dl, hematocrit 45.2 percent, creatinine 1.7 mg per dl, blood urea nitrogen 25 mg per dl and sedimentation rate 12 mm per hour; serum protein values were normal (albumin 3.4 and total protein 6.7 grams per dl). He stated that there was no family history of endocrine disorders, kidney stones or peptic ulcer disease and that he had never received radiation to his head or neck.

An exploratory operation of the patient's neck uncovered a left upper parathyroid adenoma (1.0×0.8 cm); three other normal-sized parathyroid glands were identified. The adenoma was excised and its identity confirmed by frozen section. On the first postoperative day his serum calcium level remained elevated at 10.9 mg per dl, and serum phosphorus low at 2.2 mg per dl. Because of this, he returned to the operating room. Biopsies of his normal-appearing right lower, right upper and left lower parathyroid glands confirmed that there were no abnormalities. A thymectomy and subtotal thyroidectomy were also done. A fifth parathyroid gland was present in the removed thymic tissue and no abnormalities were present. Postoperatively, he remained mildly hypercalcemic.

A year later and two years before his admission to our hospital, the patient was readmitted for persistent hypercalcemia, hypertension with polydipsia. Laboratory data included the following values: serum calcium 11.2 to 11.5 mg per dl, phosphorus 3.1 to 3.2 mg per dl, PTH 169 μIEq per ml, alkaline phosphatase 160 mU per ml and chloride 110 mEq per liter; the serum protein level was within normal limits. Arteriography suggested a possible left upper parathyroid tumor, and highly selective venous catheterization and parathyroid radioimmunoassay gave the highest PTH concentration 2,380 pg per ml (normal less than 600; R. Reitz, MD, Endocrine Metabolic

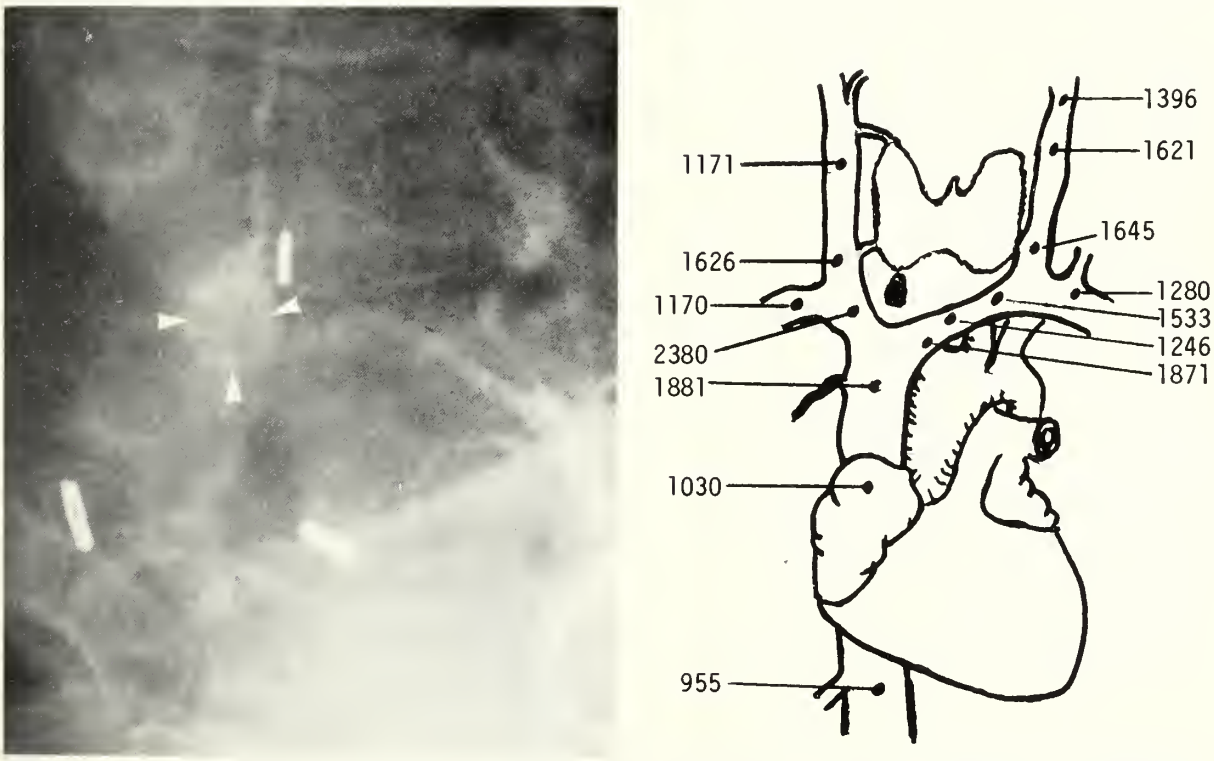

Figure 1.—Left, Arteriogram with selective injection of left thyrocervical trunk shows slight blush compatible with a parathyroid tumor or remnant thyroid tissue. **Right,** Pictorial representation of selective venous catheterization with parathyroid hormone (PTH). Numbers indicate values in pg/ml (normal less than 600 pg/ml). (PTH assays done by R. Reitz, MD, Endocrine Metabolic Center, Providence Hospital, Oakland, California.)

Center, Providence Hospital, Oakland, California) in the right innominate vein (Figure 1). A ciné-esophagram showed a small Zenker's diverticulum without other pathological features. During a second exploratory operation a chestnut brown tumor (1.0×0.8 cm) was identified in the left side of the neck at the site suggested by the arteriogram. This tumor was situated adjacent to but separate from the thyroid gland and was removed. Histological examination of the frozen section was interpreted as a probable parathyroid adenoma. No further exploration was done. After this operation, the patient remained hypercalcemic, however. The final diagnosis of the removed tissue specimen was a thyroid colloid nodule. Three days after the operation the patient was returned to the operating room for another cervical exploration and a median sternotomy. At this operation only a small remnant of thyroid was present bilaterally, the carotid sheaths were opened, and all remaining thymic tissue and pericardial fat were removed. No abnormal parathyroid tissue was identified. Final tissue diagnosis showed 29 lymph nodes, plus remnants of thymus and fat. The patient's postoperative course was uneventful, but hypercalcemia persisted. Therefore, oral therapy with phosphate (Neutra-Phos, 300 ml three times a day) and furosemide (Lasix, 20 mg twice daily) was begun to decrease his blood calcium level. He continued to do relatively well on this regimen except for dizziness and polydipsia; however, his parathyroid hormone level increased from 190 to 364 μlEq per ml (normal less than 40; Claude Arnaud, MD, Veterans Administration Medical Center, San Francisco) and his serum alkaline phosphatase level increased from 120 to 164 mU per ml. Industrial-grade roentgenograms of the hands showed subperiosteal resorption.

In a further attempt to locate the elusive parathyroid tumor, ultrasonography of the neck (Picker 80 L digital ultrasound unit, Picker Corporation, Cleveland, with a 5 MHz transducer) was done to try to localize the elusive parathyroid tumor. A nonpalpable mass measuring 1.5×1.0 cm was identified at the superior aspect of the right mediastinum at the level of the sternal notch (Figure 2). Because of the increased risk of complications while operating on a patient who has had previous parathyroid explorations, and to confirm that the mass was a parathyroid tumor, an aspiration biopsy was done, using a 23-gauge needle under ultrasonographic guidance. Findings of the cytological examination were compatible with a parathyroid tumor (Figure 3). At reoperation several days later, a second parathyroid adenoma—and sixth parathyroid gland—was located at the site indicated by ultrasonography (Figure 4) and was removed. His serum calcium level decreased to 8.1 mg per dl on his third postoperative day, and his serum phosphorus level measured 2.6 mg per dl. His symptoms of polydipsia disappeared, his voice remained normal and subjectively the patient felt better. Three months following the operation his serum calcium level was 8.6 mg per dl.

Discussion

This case is of interest because it points out the difficulties in managing patients with multiple parathyroid adenomas and more than four para-

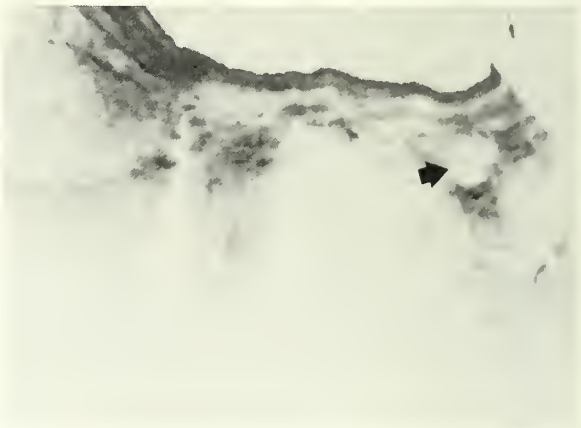

Figure 2.—A longitudinal sonogram shows a mass **(arrow)** of low echogenicity, the parathyroid adenoma, just above the sternal notch, 0.5 cm to the right of midline. No thyroid tissue is present. The dot-to-dot distance is 1 cm.

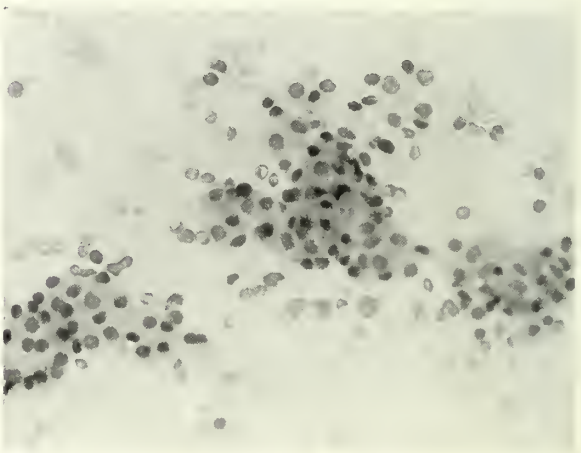

Figure 3.—Cytological specimen showing mildly atypical cells consistent with parathyroid tumor.

Figure 4.—Photograph of a parathyroid adenoma weighing 2.0 grams, which has been bivalved along long axis.

thyroid glands. It also demonstrates the limitations of tests in locating parathyroid tumors and the difficulty of making accurate histological diagnoses of parathyroid tissue on frozen section. Also of interest are the diagnostic problems encountered in a patient with a bladder tumor, a tumor known to secrete a PTH-like substance and cause ectopic hyperparathyroidism.[8] The most important reason for reporting this case, however, is that it shows that a probable parathyroid tumor as localized by ultrasonography can be identified by percutaneous aspiration biopsy and cytological examination, a simple procedure with minimal complications.

Multiple parathyroid tumors are a well-known cause of persistent hyperparathyroidism and occur in 4 percent of patients with primary hyperparathyroidism.[9] Having more than four parathyroid glands has been reported to occur in as many as 6 percent of the population.[10] The coexistence of multiple parathyroid adenomas and six parathyroid glands, however, is distinctly unusual.

When this patient was originally seen, metastatic transitional carcinoma of the bladder was considered a possible cause for his hypercalcemia and elevated levels of parathyroid hormone. Evidence favoring primary hyperparathyroidism rather than ectopic hyperparathyroidism included the following: no evidence of residual bladder tumor; no loss of weight; no abnormalities noted on a bone scan and x-ray study of the chest; hematocrit and sedimentation rate within normal limits, and appropriate serum PTH level for someone with primary hyperparathyroidism and somewhat higher than that usually found in patients with ectopic hyperparathyroidism.[11,12]

The arteriogram that was used to localize his parathyroid tumor after his initial parathyroid operation was misleading. A thyroid scan had been done to improve the diagnostic accuracy of arteriography as recommended by Kountz and co-workers,[13] but there was little uptake of radioactive iodine by thyroid tissue. The misinterpretation of the frozen section specimen at the second operation complicated his treatment because the operation was discontinued before the real parathyroid adenoma was discovered. Occasionally, it is difficult to determine histologically whether a tumor is of thyroid or parathyroid origin. It is important to bear in mind that colloid-like material and acini may be seen in a parathyroid adenoma.[14] In retrospect, the highly selective venous catheterization in conjunction with PTH radioimmunioassay correctly predicted the position of the parathyroid adenoma.

Parathyroid ultrasonography, which has recently been recommended for localizing abnormal parathyroid glands, was very helpful in this patient.[1-4] Aspiration cytology has been recommended for the evaluation of thyroid nodules and is reported to be as accurate as a diagnosis by frozen section.[15-17] A relatively large parathyroid adenoma was expected because of high PTH levels in our patient and because he did not have renal failure. Also, there is usually a good correlation between the size of the parathyroid gland and the degree of elevation of PTH hormone.[11]

Summary

A patient had persistent hyperparathyroidism despite the removal of a parathyroid adenoma and histological confirmation of four other normal parathyroid glands. His elusive second adenoma—and sixth parathyroid gland—was located by aspiration biopsy and confirmed by cytological examination. This knowledge greatly facilitated the surgical removal of the second tumor. Thus, ultrasonography and aspiration biopsy cytology may be helpful in finding the exact location of parathyroid tumors in selected patients with primary hyperparathyroidism.

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Achievement of Total Thyroidectomy

MANY PEOPLE SAY that perhaps a total thyroidectomy is . . . impossible. So we made a study in which we did postoperative scans in a group of patients and found that 87 percent had an uptake equivalent to the background uptake, which means they had virtually a total thyroidectomy. . . . I think it's higher now. We advocate total thyroidectomy for invasive cancer of all types—meaning that they have broken through the capsule but they are not microcancers, or that they have shown evidence of invasion either of thyroid tissue or extrathyroid tissue. The operation can be done safely and it can be done completely.

—JOSEPH N. ATTIE, MD, *New York City*

Extracted from *Audio-Digest Surgery*, Vol. 28, No. 8, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Fallacies and PPI's

To the Editor: Dr. Goyan's comments on patient package inserts (PPI)[1] in the May 1981 issue were interesting, and I agree with most of them. However, certain points need clarifying.

The third fallacy (patients don't need PPI information), of the 14 he discusses, has little to do with whether patients' compliance will be enhanced by PPI's. Many doctors feel that PPI's will *decrease* patient compliance by frightening them away from taking medicine. Who would take aspirin after reading a complete list of possible side effects, including bleeding, ulcer and life-threatening anaphylaxis? Patients want information on how to take drugs (with or without food, with or without other medicines, AM or PM) and common side effects. But what purpose is served by listing dozens of reactions that are rare, are only occasional or occur in less then 1 percent of cases? And how could a physician prescribe a medication for a purpose not listed on the PPI? All he would hear would be, "Why are you giving me an arthritis drug for menstrual cramps?" or "This drug treats *Trichomonas,* not *Giardia,* so it can't do me any good."

Dr. Goyan's fallacy is that patients are as sophisticated as doctors in their ability to sift through drug information in PPI's. Physicians must frequently edit information for their patients to put it in a form they can understand and accept.

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Drugs Associated With Retroperitoneal Fibrosis

To the Editor: I read with interest "Retroperitoneal Fibrosis as a Cause of Fever of Undetermined Origin" in the April issue.[1] In 1948 idiopathic retroperitoneal fibrosis was first described as a clinical entity. Most often the patient is a middle-aged man with primary symptoms of backache, anorexia and weight loss in whom oliguria and azotemia subsequently develop.[2] This symptom complex is seen with fibrous tissue growth in the retroperitoneal space which encroaches upon nearby organs and blood vessels. The fibrous tissue appears as a glistening, white, woody hard plaque.

Dr. Byrd's case description is atypical in many respects. Abdominal or back pain, absent in this patient, occurs in most published cases. The localized fibrous tissue mass without ureteral involvement is not characteristic. Usually one or both ureters are encased by contracting fibrous tissue which is usually confined to the limits of Gerota's fascia.[3] Most reports of this disorder are found in the urologic literature because patients always present with ureteral obstruction and frequent azotemia, and are quickly referred to a urologist. Retrograde placement of ureteral catheters is easily accomplished in spite of the fibrosis surrounding the ureters. Surgical lysis and peritonealization of the ureters reverses the azotemia and frequently relieves the pain. Although a hypochromic anemia is characteristic in idiopathic retroperitoneal fibrosis, it is usually not so severe as to require transfusions.

Many pharmacologic agents have been associated with the development of retroperitoneal fibrosis: methylsergide, hydralazine,[4] ergotamine tartrate,[5] methyldopa,[6,7] aspirin-phenacetin-codeine analgesics,[8,9] oxyprenolol,[10] atenolol,[11,12] lysergic acid diethylamide (LSD),[5] dextroamphetamine, ephedrine and strychnine.[3] Since this list of drugs appears to involve vasoactive substances, it has led to a hypothetical pathogenic mechanism. The prolonged and repeated arteriolar vasoconstrictions and vasodilations may lead to perivascular edema, transudation of plasma content and the initiation of the sustaining fibroblastic response.[3] We must realize the possibility that many drugs commonly prescribed may conjugate with antigens, incite a hypersensitivity response and lead to retroperitoneal fibrosis. Since retroperitoneal

fibrosis represents a reversible cause of renal failure, it would be wise to keep this clinical picture in mind.

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Use of Barbiturate Suppositories

To the Editor: We thought it relevant to present the experience of one of us (L.E.S.) with the use of barbiturate suppositories as an alternative to orally given barbiturates:

In my community it is not an infrequent occurrence that there is a death associated with alcohol use and barbiturates. There is often the query, was this accidental or suicidal? Did the victim succumb from repeated ingestion of an oral barbiturate while intoxicated from alcohol and so not recall the number of pills ingested? The therapeutic to lethal ratio varies in sedative/hypnotic barbiturates, especially when associated with alcohol use. This makes accidental death feasible and intentional suicide easy.

In general, it is difficult to cure alcohol abuse as well as withdraw barbiturates from patients who have been using them chronically for sleep for many years. It is that kind of patient, albeit a common problem in our society, for whom I began prescribing rectal suppositories 15 years ago. Since that time I have witnessed no *accidents* or suicides in my practice. Further, I have extended the limited prescription of rectal suppositories to patients who have been on oral barbiturates but who are emotionally unstable and possibly suicidal. The abuse potential is much lower with rectal suppositories, and with my patients using them instead of oral barbiturates, I sleep better.

The Los Angeles County Coroner has never seen a death from overdose with rectal suppositories, although patients have taken them orally with suicidal intent. The reason is apparently due to poor and delayed gastrointestinal absorption. The use and misuse of sleeping pills cannot be changed overnight. The use of rectal suppositories does not curtail the problem, but it may alter it so that the consumer can live with it more safely.

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Hyperventilation Versus Bicarbonate Therapy for Alkalinization in Tricyclic Antidepressant Overdose

To the Editor: Hoffman and McElroy's recent article "Bicarbonate Therapy for Dysrhythmia and Hypotension in Tricyclic Antidepressant Overdose"[1] was of great interest.

It is well recognized that alkalinization, either by bicarbonate or hyperventilation, can dramatically reverse the manifestations of tricyclic antidepressant overdose (TCA) toxicity. There remains some controversy, however, as to whether bicarbonate or hyperventilation is the preferable method of achieving this.

Kingston[2] recently described treatment with hyperventilation in similar cases, and felt that hyperventilation may have some advantages over bicarbonate. Hyperventilation may be immediately effective compared with the potential delay of bicarbonate infusion. The alkalemia induced by bicarbonate changes only the extracellular pH, because cell membranes are poorly permeable to hydrogen and bicarbonate compared with carbon dioxide. The rise in extracellular pH may decrease ventilation, diminishing the rise in pH; and may actually paradoxically decrease intracellular pH. In addition, the hazard of sodium overload may predispose to pulmonary edema. And, last, metabolic alkalosis induced by bicarbonate makes it more difficult to wean patients from mechanical ventilation, a common problem in intensive care units. Overall, I think the evidence favors hyperventilation as the method of choice.

I would also like to comment on antiarrhythmic drug use during TCA overdose.

Lidocaine has its proponents[3] and detractors.

However, I find no evidence, in the reference cited,[4] that lidocaine potentiates the hypotension of TCA overdose. Clinically, this has not been a problem with lidocaine, though its efficacy remains a debatable point.

The statement that propranolol is contraindicated is not true in all cases. The authors were referring to the catechol-depletion stage of TCA overdose, since in this instance hypotension can be exacerbated.[5] However, propranolol is very effective in the treatment of tachyarrhythmias due to TCA overdose,[6-9] since they are due to catechol release.

Bretylium is a drug that deserves further study. It does not impair conduction[6] or decrease cardiac output.[10] It does cause release of catechols, actions of which might be heightened by TCA inhibition of their reuptake.[6] Bretylium has been reported to be useful in quinidine toxicity, a closely akin clinical syndrome.[10,11]

Clearly, this is a complex area, about which there is not uniform agreement. I'm sure the readership of the WESTERN JOURNAL appreciates that there are varying opinions on the subject.

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Diet and Psoriasis

TO THE EDITOR: In his letter in the April 1981 issue[1] Dr. Rapaport correctly concludes that dietary manipulation has not been shown to be effective in the management of psoriasis. However, the inclusion of the report by Zackheim and Farber[2] in a group of references relating to dietary studies that were criticized as failing to recognize the generally beneficial effect of hospital admission on psoriasis is misleading.

In fact our study concluded that although patients receiving regular diets and those receiving low protein diets all initially improved (two subsequently relapsed) there was no significant difference in the degree of improvement between the two groups. In a second hospital-based study[3] patients with a low-calorie diet actually did worse than those on a regular diet. Additionally, while the disease in four of eight patients receiving a regular diet improved, in two it was unchanged and in two it became worse.

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Special Article

Refer to: Clever LH: Health hazards of hospital personnel. West J Med 135:162-165, Aug 1981

Health Hazards of Hospital Personnel

LINDA HAWES CLEVER, MD, *San Francisco*

Health care workers historically have faced serious health problems, such as exposure to patients with tuberculosis. For hospital personnel today, a number of hazards exist. These range from toxic substance exposure to safety hazards presented by patients themselves.

IN CALIFORNIA there are 510 community hospitals. These hospitals employ more than 250,000 people, about 1 percent of whom are physicians, 20 percent registered nurses (RN), 8 percent licensed vocational nurses (LVN) and 71 percent others.[1] These personnel face a number of health hazards. Some hazards are ancient, such as tuberculosis; others reflect currently used, sophisticated diagnostic and treatment measures.

Bernardino Ramazzini, an early occupational medicine specialist, called attention to diseases of health workers in the 18th century. He stated that diseases of midwives, for example, included dermatitis, exhaustion and the "French disease" and hoped that the new practice of laboring and delivering in bed would soon spread to Italy. This would spare midwives the uncomfortable posture and constant bathing of their hands in lochia required by the labor chair.[2]

Special problems faced by hospitals and medical centers today still include infection and effects produced by patients themselves. In addition, the consequences of research on the frontiers of biology (unusual organisms, recombinant DNA) and specific chemicals (ranging from formaldehyde to perchloroethylene) must be faced and assessed. Furthermore, hospital workers share the hazards of those who work in restaurants, factories, offices and construction sites. These include exposure to ionizing radiation, microwaves, solvents, noise and asbestos. The impact of shift work and stress is also notable.

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Usual Work-Related Problems

Actual experience with occupational injury and disease in hospitals shows that most recognized work-related problems are not exotic. A survey published in 1975 and dealing with California reported that almost half of lost-time work injuries to RN's, representing about 13 percent of all injuries and illnesses to hospital workers, were from strain or overexertion. At least 86 percent of these injuries were related to patient care; almost 40 percent affected the back. Almost 20 percent of lost-time work injuries resulted from mishaps on unsafe, wet, littered floors. Nearly half of all lost-time injuries to RN's were directly involved with patient care. Interestingly, infections such as hepatitis, tuberculosis, childhood diseases and staphylococcal disease, caused only 6 percent of lost-time problems.[3] Almost 40 percent of injured hospital workers were LVN's, nurses' aides or nursing attendants. It is of interest that in California private hospitals, LVN's and nurses' aides

had more work injuries than any other occupational group. Of people with lost-time injuries, 15 percent worked in housekeeping departments, 14 percent worked in kitchens, 9 percent were clerical workers and 6 percent were maintenance workers. Some 26 percent of injuries not involving RN's were directly related to patients; more than 20 percent were slips-and-falls; 45 percent were strains or overexertion; 37 percent of all lost-time injuries involved the back. To put this in perspective, the incidence of all occupational illness and injury was slightly higher in California hospitals (11.5 per 100 full-time workers) than in hospitals elsewhere in the United States (9.6 per 100 full-time workers) but slightly lower than in the California non-farm private sector (12.1 per 100 full-time workers).[4]

Aside from musculoskeletal injuries, one of the most frequent topics of conversation about injuries in hospitals is the role of stress. According to the 1977 National Institute of Occupational Safety and Health (NIOSH) occupational stress conference, stress-related disease was defined as coronary heart and artery disease, high blood pressure, ulcers and nervous disorders. Of the 40 occupations with the highest incidence of stress-related disease, 6 were in the health care field. Clinical laboratory technicians were fourth highest (after laborers, secretaries and inspectors). Of the 12 occupations with highest mental health admission rates, five were in health-related fields. These were health technologists, LVN's, clinical laboratory technicians, nurses' aides and dental assistants.[5] These findings have received widespread attention from the press, but the definition of stress-related disease is not universally accepted nor has a cause and effect relationship been established.

Chemical Hazards

Chemical hazards can be found throughout a hospital, from the laboratory to the operating room to central supply. Picric acid, used in Bouin's fixative and trichrome stain, is highly explosive in the crystalline form. A West Coast dental school was evacuated recently while the local bomb squad removed long-neglected picric acid from several locations.[6] Benzene, bone marrow toxic, and mercury, known for its nervous system, skin and renal effects, may be found in laboratories, depending upon analytical methods used. Formaldehyde, used in dialysis units, may cause eye, respiratory and dermatologic problems, and other adverse effects. Ethylene dichloride, known for its renal, hepatic, dermatologic, central nervous system and corneal effects; osmium tetroxide, a potent irritant; and other irritants that may induce central nervous system problems (xylene, isopropyl alcohol) may be found in cytology laboratories. Perchloroethylene (tetrachloroethylene), known for its central nevous system, liver and skin effects, may well be used in hospital print shops. Operating rooms, a source of infection, are also a site for waste anesthetic gases. The latter are the subject of a 1977 NIOSH criteria document which reviews the gases' possible reproductive, renal, hepatic, central nervous system and carcinogenic effects.[7]

Ethylene oxide (ETO), used to sterilize equipment that cannot be autoclaved, was linked with the development of cancer in female mice in one report.[8] It has also been the focus of recent epidemiological and clinical research. The study group has found as increased incidence of chromosome aberrations in employees exposed to ethylene oxide compared with those not exposed. This appears to be statistically significant. These aberrations include an increased number of sister chromatid exchanges in those who also have increased quadriradial exchanges. These changes have not decreased in workers removed from exposure for one year. Studies are now underway to evaluate the effects of ethylene oxide on male fertility. At this time, the recommendation is to limit exposure to a 10-ppm time-weighted average for eight hours. Employees are also provided respiratory protection to decrease exposure further.[9] The ETO story is just beginning to unfold and is an example of the tantalizing research opportunities in the area of hospital health.

Infectious Diseases

Infection control is an important matter for employees and patients. Hepatitis B (HBV) is the major hepatitis threat to hospital employees who come into contact with patient blood (the chief culprit) and secretions. The current consensus is that patients with HBV pose more of a danger to employees than vice versa, although scattered employee-to-patient reports have appeared.[10] Hemodialysis, oncology, blood bank and venipuncture personnel are at highest risk. Prudent use of gloves, proper needle use and disposal, and passive immunization are useful control measures.

Active immunization holds promise for better control.

Tuberculosis surveillance for hospital employees is required by most state health codes but immunization for childhood disease is not. Rubella, because of recent hospital employee outbreaks and because of special risks to fetuses and adults, has been spotlighted recently.[11] The only sure break to infection spread, vaccination, has not always led to complication nor increased absenteeism.[12] Enteric pathogens and venereal diseases are more frequently associated with life-style than with hospital employment but still may be rather commonly seen and troublesome.

It should go without saying that for workers with direct or indirect patient contact, the patients themselves are often the injurious agents. Thus, patients are the source of orthopedic problems, infections and stress. The good health of hospital workers is requisite to the health of these patients, however, and is therefore of profound importance.

Identifying and Eliminating Hazards

Concern and awareness are not sufficient to protect the health of hospital workers. Precise knowledge of workplace hazards will allow modifications and proper surveillance. Acquisition and analysis of material safety data sheets (MSDS) for substances used in departments such as maintenance, the laboratory, environmental services and the print shop are crucial. This can be rather easily accomplished: the purchasing department can request MSDS's from suppliers and transmit the information to hospital health and safety personnel for review and recommendations. Environmental sampling is also important. The existence of fans, for example, does not mean that they function adequately. Therefore, air sampling for toxic substances must be done.

Identifying and eliminating hazards before they are established and encouraging the purchase of equipment that can decrease accidents can have a dramatic impact on hospital health. This prepurchase evaluation of new equipment and materials can be achieved by seating health and safety personnel on medical capital equipment and product evaluation committees. Analyzing sick call and workers' compensation data can detect actual or potential work-related problems. Similarly, walk-around tours of all hospital departments by health and safety personnel can be enormously valuable. Injury statistics suggest that body mechanics training may be indicated in an attempt to ameliorate orthopedic problems.

Employees who face special hazards should have special protocols for their medical surveillance so that early intervention can occur. Thus, laboratory, central supply, engineering, operating room and dialysis unit personnel would have distinctive evaluations. Because of their exposure to noise in boiler rooms, for example, engineers should have baseline and periodic hearing evaluations. Conversely, dialysis workers need preplacement and periodic evaluation of their liver function and hepatitis status (susceptibility, stage of infection, infectivity). Assessment of radiation exposure in operating and emergency rooms and intensive care personnel may be indicated.

Personal health assurance is also important. This can include battalion aid station-type sickness care, fitness programs (employees could use the physical therapy department during the lunch hour), smoking cessation, employee-assistance programs, hypertension screening and follow-up, and even listing calories and sodium content in cafeteria menus.

Comprehensive Programs Within Hospitals

Because the health of hospital workers has not been a major concern of regulatory or research organizations and has only rather recently received attention from employees themselves, few hospitals have developed comprehensive health programs for their employees.[13] Development of these programs depends upon enthusiastic support from the highest level of a hospital's board and administration, which could require, for example, supervisorial accountability for health and safety training and compliance. Analysis of the cost-effectiveness of the employee-assistance program and of the possible impact that an effective employee-health program can have on workers' compensation and health insurance costs can assure and augment this support.

Membership and leadership of the safety committee, establishment of departmental safety committees, union participation in health and safety activities, participation of health and safety personnel on pertinent hospital committees (infection control, risk management, and radiation safety in addition to the aforementioned), and interhospital cooperation and sharing of qualified health and safety personnel are all important details. These details need to be jointly addressed by medical staff, administration, employee repre-

sentatives, and health and safety personnel. In this way, action can be added to concern, awareness and knowledge so that the health of hospital personnel can be maintained and enhanced.

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Malignant Degeneration of Giant Hairy Nevus

DR. KREMENTZ: There's a debate about what percent of patients with giant hairy nevus will develop melanoma—it varies in the literature from 5 percent to 40 percent. I think most people like to get them removed, if you can do it without destroying the child psychologically.

DR. MCBRIDE: We haven't been able to get a handle on the percentage of malignant degeneration. Everybody has gotten so used to the darn thing [hairy nevus] that the malignant degeneration occurs and isn't noticed . . . They should come off.

DR. KREMENTZ: We're seeing more of these kids coming in with malignant development in congenital nevus in the last two years. I think we've had three in our center. One was controlled and two have died of disease. It can be a very devastating tumor when it takes off.

—EDWARD T. KREMENTZ, MD, *New Orleans*
CHARLES M. McBRIDE, MD, *Houston*

Extracted from *Audio-Digest Surgery*, Vol. 28, No. 10, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Zemlyn S, Wilson WW, Hellweg PA: A caution on iodine water purification (Information). West J Med 135:166-167, Aug 1981

Information

A Caution on Iodine Water Purification

SEYMOUR ZEMLYN, MD
WILLIAM W. WILSON, PhD
PAUL A. HELLWEG, MS
Los Angeles

IODINE IS the most effective agent for purifying backcountry water. Tetraglycine hydroperiodide tablets have been sold by camper and hiker suppliers under several brand names (such as Potable-Aqua and Coughlan's) for many years, providing a safe, convenient way to disinfect suspicious water for drinking.

Iodine in the crystalline form has been advocated as a safer, more effective means of accomplishing this goal.[1] However, the safety of crystalline iodine has been overstated, and a potentially lethal hazard exists in this technique.

To use crystalline iodine, a vial containing 4 to 8 grams of crystals is carried into the backcountry. When water is to be purified it is introduced into the vial which is vigorously shaken. A small amount of the solution is then introduced into the water in a canteen or container for drinking. Because iodine crystals are sparingly soluble the resultant supernatant will generally provide the optimal concentration of 8 to 16 parts per million of iodine.

One proponent states that although iodine is a poison "no fatality from ingestion of less than 15 grams of iodine has been reported."[1] This may well have been a clerical error. Chemical and pharmaceutical texts list the probable lethal dose of iodine as 2 to 4 grams,[2-4] and fatalities have been reported with less than 2 grams.[5,6] This means that a hiker would carry about 2 to 4 times the lethal dose in his water-purifying vial.

From the Department of Radiology, Los Angeles County/University of Southern California Medical Center (Dr. Zemlyn); Exploratory Chemistry and Laser Programs, Rocketdyne, Canoga Park, California (Dr. Wilson), and the Department of Recreation and Leisure Studies, California State University, Northridge, California (Mr. Hellweg).

Reprint requests to: Seymour Zemlyn, MD, 18411 Clark Street, Suite 101, Tarzana, CA 91356.

The technique of decanting (the pouring off of a supernatant from a less soluble component) is not acceptable by the California State Board of Pharmacy. An intervening filter is recommended to improve the safety and reliability of the procedure. If this is not recommended for skilled pharmacists it would seem less appropriate in the hands of hikers and campers. Most alarmingly we discovered some girl scouts practicing this technique of iodine water purification. The risk of disaster multiplies in this group because of lesser mechanical skills, less mature judgment and a lower lethal dose. The accidental introduction of iodine crystals into the drinking water may result in a potentially lethal situation.

The introduction of a filter could obviate this hazard. Iodine is very reactive and chars or stains most common filter materials. Laboratories use Teflon filters for this purpose. The pore size must be small enough to prevent the passage of crystalline material. Such a filter is not inexpensive and is not commonly available to backpackers.

Tetraglycine hydroperiodide tablets provide a predictable dose of iodine and are easily handled. One tablet when dissolved in one liter of water provides a concentration of 8 parts per million. Chang[7] showed that almost all water can be made safe for drinking with this dose. Two tablets may be safely used for heavily polluted water. An entire bottle of 50 tablets contains only 0.4 gram of iodine and accidental overdose cannot occur.

The tablets have been said to be less stable than the crystals.[1] In fact, under most circumstances the opposite is true. Iodine crystals sublime (pass directly from solid to gas without a liquid phase) readily. At 25°C (77°F) the vapor pressure of tetraglycine hydroperiodide is 0.0013 torr (mm of mercury)[8] and crystalline iodine is 0.305 torr.[9] If these substances are exposed in an enclosed area, such as a two-man tent overnight, it can be calculated that the much greater vaporization of the crystalline material could result in a toxic level of iodine inhalation from the resultant fumes. This is not possible with the tablets.

It has been claimed that the tablets deteriorate rapidly.[1] Morris and Chang,[8] however, showed that tetraglycine hydroperiodide tablets stored in amber, wax-sealed bottles at 38°C (100°F) and 49°C (120°F) at 100 percent humidity do not deteriorate for as long as 24 weeks. Exposed tablets spread in a single layer at 60°C (140°F) for seven days retained 60 percent of their original

TABLE 1—*Comparison of Crystalline Iodine and Tetraglycine Hydroperiodide Tablets*

	Crystals	*Tablets*
Pack quantity	4-8 grams (2-4 times lethal dose)	50 tablets (1/5 lethal dose)
Solubility	Poor (temperature dependent)	Excellent
Shelf stability	Excellent	Good
Stability, exposed to air	Poor (sublimes)	Excellent
Vaporization	Toxic fumes	Negligible vaporization
Administration	Complicated (decanting required)	Simple (tablet dose)

iodine activity. If crystalline iodine were subjected to these conditions it would totally vaporize within 24 hours.

Conclusion

Iodine is a convenient and effective water purifier. The use of crystalline iodine, however, should not be recommended; it may be hazardous. Tetraglycine hydroperiodide tablets are safer, more stable, convenient and easier to use (Table 1). Such tablets would seem to be the method of choice for purifying suspect backcountry water for drinking. If crystalline iodine is used a suitable filter should be introduced between the crystal-containing solution and the drinking water container.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

THE COMPREHENSIVE HANDBOOK OF BEHAVIORAL MEDICINE—Edited by James M. Ferguson, MD, Medical Director, Gifford Mental Health Center, Assistant Professor of Psychiatry, University of California, San Diego, School of Medicine and Department of Psychiatry, VA Medical Center, La Jolla; and C. Barr Taylor, MD, Assistant Professor of Psychiatry, Stanford University Medical Center, Stanford. Volume 1: SYSTEMS INTERVENTION, 304 pages, 1980, $30.00; Volume 2: SYNDOMES & SPECIAL AREAS, 350 pages, 1981, $30.00; Volume 3: EXTENDED APPLICATIONS & ISSUES, 344 pages, 1980, $30.000. SP Medical & Scientific Books, 175-20 Wexford Terrace, Jamaica, NY 11432.

For those who apply the reductionist's approach to medical practice, *The Comprehensive Handbook of Behavioral Medicine* has a great deal to offer. The book is comfortably categorized into old and well-accepted subdivisions of medical disciplines that deal with the psyche and soma. However, for those who believe that the teachings of George Engel[1] represent the new wave of behavioral science, the three-volume work edited by Ferguson and Taylor is a disappointment.

The stated goals of the editors are to have their book demonstrate the "application of applied behavioral analysis and behavioral therapy techniques to medical problems." In an excellent introduction, the editors offer in a well-organized format the history and definitions needed to obtain an understanding of the behavioral sciences. Their review of behavioral theory and principles includes clarification of behavioral antecedents, consequences of behavior, and behavior therapies.

The book is addressed to practitioners and researchers; however, in general, the chapters written by qualified contributors are richer in research data, instruments and references than in pragmatic information for practicing physicians.

Some of the highlights of the book are sections on adherence, compliance, biofeedback and relaxation. Behavioral concepts are well presented in chapters that deal with modification or management of smoking, alcoholism, asthma, obesity, chronic pain, skin disorders, hypertension and enuresis.

As indicated in the introduction to the review, the major disappointment in the book is its failure to deal with the patient within the context of an integrated biopsychosocial model (the patient within the context of family and community). The indices for Volumes 1 and 2 do not list the family, social support or community. A follow-up of family and social group items in Volume 3 revealed a half-page on the influence of the family on the patient with a final caution: "[social] support was stressful for certain patients."

That the patient's behavior is profoundly influenced by family and sociocultural determinants is evidenced by a growing literature that is not included in the book under review. For example, the chapter on sexuality fails to deal with family dysfunction as a factor in sexual dysfunction. In the chapter on human performance in athletics, little attention was directed to anxiety as a consequence of pressure caused by peers, parents and coaches. Furthermore, the psychological trauma induced by persistent athletic failures that results in long-term problems with self-esteem is also not found in this section.

Family, community and cultural issues (Kleinman)[2] that pertain to behavioral problems in circulatory disease (Medalie),[3] pregnancy (Nucchols)[4] and asthma (Minuchin)[5] were some of the areas neglected in *The Comprehensive Handbook of Behavioral Medicine.*

Since the editors wished to address the subject of behavioral science as it applies to medical problems, a section on physician/patient interaction should certainly have been included.

It is the impression of this reviewer that Ferguson and Taylor have put together a potpourri of chapters on behavioral medicine that will provide students of the field with valuable references (up to 1978). The reader will not, however, gain a "comprehensive" view of the behavioral sciences nor will the reader find the book a resource for understanding the behavior of the patient within the context of family and community.

GABRIEL SMILKSTEIN, MD
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Department of Family Medicine
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* * *

GENERAL OPHTHALMOLOGY—Ninth Edition—Daniel Vaughan, MD, Clinical Professor of Ophthalmology, University of California, San Francisco; and Taylor Asbury, MD, Professor of Ophthalmology, Director, Department of Ophthalmology, College of Medicine, University of Cincinnati; illustrated by Laurel V. Schaubert. Lange Medical Publishers, Drawer L, Los Altos, CA (94022), 1980. 410 pages, $15.00.

General Ophthalmology is likely the textbook of ophthalmology most utilized by medical students, and with good reason. The latest edition draws on the experience of 20 years since the first edition appeared. Unlike some texts that deteriorate in succeeding editions, this one incorporates significant new material in each new edition and thus truly improves with age. Accordingly it is useful not only to medical students but to physicians who wish a quick reliable, readable reference.

The Ninth Edition is increased to 410 pages, compared with 379 for the preceding edition. It covers such current topics as electrophysiologic testing of visual function, genetic ophthalmology, and the CT scan in ophthalmology. The practical, useful nature of this text is indicated by the fact that it begins with a table summarizing the differential diagnosis of the red eye, and it concludes with a glossary to help in translation of those many illegible abbreviations used by ophthalmologists in consultation notes. Neuroophthalmology and ocular disorders associated with systemic disease receive appropriately heavy emphasis. Particularly useful now in medical school curricula lacking required ophthalmology instruction is a chapter on how to carry out ophthalmoscopic examination. Illustrations and references are excellent. The Ninth Edition is to be recommended with enthusiasm.

ROBERT S. HEPLER, MD
Professor of Ophthalmology
Jules Stein Eye Institute
Department of Ophthalmology
UCLA Center for the Health Sciences
Los Angeles

UTAH STATE MEDICAL ASSOCIATION

USMA 86th Annual Meeting

eptember 9 through September 11, 1981 • HOTEL UTAH, SALT LAKE CITY, UTAH

VEDNESDAY, SEPTEMBER 9

ourse No. 1

ROBLEMS IN DERMATOLOGY

00 am

oderator:
ONARD J. SWINYER, MD
inical Assistant Professor,
partment of Dermatology, University of Utah
lt Lake City

ROBLEMS IN DERMATOLOGY—HOW WOULD YOU VALUATE AND TREAT THIS CASE?

ase format to discuss the listed common rmatoses)

Contact Dermatitis	10. Warts
Psoriasis	11. Congenital Hairy Nevus
Basal Cell Carcinoma	12. Oral Ulcers
Acne Vulgaris	13. Acne Rosacea
Herpes Simplex	14. Melanoma
Candida Vulvovaginitis	15. Alopecia Areata
Scabies	16. Seborrheic Keratoses
Port Wine Stain	17. Pyogenic Granuloma
Actinic Keratoses	18. Tinea Pedis and Id

rticipants:
ONARD J. SWINYER MD
lt Lake City
HN J. ZONE, MD
sistant Professor of Internal Medicine
vision of Dermatology
iversity of Utah College of Medicine
lt Lake City
RALD G. KRUEGER, MD
sociate Professor of Internal Medicine
vision of Dermatology
iversity of Utah College of Medicine
lt Lake City

ourse No. 2

STHMA, EMPHYSEMA, CHRONIC RONCHITIS—AN UPDATE FOR THE RIMARY CARE PHYSICIAN

-Moderators:
T. CHRISTENSEN, MD
sistant Clinical Professor of Pediatrics
iversity of Utah College of Medicine
d
ivate Practice, Allergy
lt Lake City
BERT O. CRAPO, MD
sistant Professor of Medicine
iversity of Utah College of Medicine
rector, Pulmonary Laboratories, LDS Hospital
lt Lake City

30 am

PD PATHOPHYSIOLOGY: Historical and ysical Highlights
HENRY WILLIAMS, JR, MD
ofessor of Medicine, Pulmonary Division
bert Einstein College of Medicine
rector, Chest Service
onx Municipal Hospital Center
onx, New York

Wednesday (continued)

9:15 am

OBJECTIVE MONITORING OF PATIENTS WITH OBSTRUCTIVE AIRWAY DISEASES
RONALD B. GEORGE, MD
Professor and Deputy Head of Medicine
Chief, Pulmonary Diseases Section
Chief of Medicine Service
Shreveport VA Hospital
Shreveport, Louisiana

9:40 am

BLOOD GASES—When to Order, How to Interpret
ALAN H. MORRIS, MD
Associate Professor of Medicine
University of Utah College of Medicine
Director: Intermountain Respiratory Intensive Care Unit
LDS Hospital
Salt Lake City

10:00 am

COFFEE BREAK

10:15 am

MANAGEMENT OF AIRWAY OBSTRUCTION
RONALD B. GEORGE, MD
Shreveport, Louisiana

11:00 am

BASIC PRINCIPLES OF THERAPY IN COPD
M. HENRY WILLIAMS, JR, MD
Bronx, New York

11:35 am

QUESTIONS AND ANSWERS—PANEL DISCUSSION

12:15 pm

LUNCHEON

ROTATING CONCURRENT CLINICAL WORKSHOPS

2:00 pm to 5:00 pm

Each one-hour workshop will be repeated three times so that participants can attend each workshop. The enrollment is limited in each workshop so that the participant can have a personal, clinical interaction with the workshop leader.

2:00 pm

Workshop A

SPIROMETRY: Devices, Uses, Misuses—Case Presentations
Team Leader:
M. HENRY WILLIAMS, JR, MD
Bronx, New York

Workshop B

ARTERIAL BLOOD GASES—Sputum Analyses
Team Leader:
ROBERT O. CRAPO, MD
Salt Lake City

Workshop C

COPD CASE PRESENTATIONS: Bronchial Asthma, Chronic Bronchitis, Emphysema (Emphasis on Diagnosis and Management)
Team Leader:
RONALD B. GEORGE, MD
Shreveport, Louisiana

Wednesday (continued)

REGISTRATION: This workshop on chronic obstructive pulmonary disease is a free standing program in the Utah State Medical Association Annual Scientific Sessions. There are two ways to register for the workshop.

(a) Registration for workshop only: Participants can register for the one-day workshop only. Registration fee is $15.

(b) Registration for full USMA Meeting: Participants who are registered for the full USMA Meeting ($50) can attend the workshop without additional registration fee. Participants may register in advance or at the registration desk in the Hotel Utah.

Attendance at the workshop will qualify the participant for 6½ hours of Category I CME credit.

Course No. 3

PERSPECTIVES IN DRUG AND ALCOHOL ABUSE

Moderator:
STEVEN D. MINTON, MD
Medical Director, Newborn Services
Utah Valley Hospital
Provo, Utah

8:30 am

MAGNITUDE OF SUBSTANCE ABUSE (United States and Utah)
BRUCE H. WOOLLEY, PhD
Professor, College of Biological Sciences
Brigham Young University
Provo, Utah

9:10 am

DOCTOR, I'VE BEEN NERVOUS—Office Visit Scenario
JOHN N. CHAPPEL, MD
Professor of Psychiatry
School of Medical Sciences
University of Nevada
Reno, Nevada

9:50 am

OPTIONS TO PRESCRIPTIONS
ROD GWALTNEY
State Division of Alcoholism and Drugs
Salt Lake City
and
EILEEN R. OCHSE
Director of Education, Prevention, and Training Unit
Division of Alcoholism and Drugs
Salt Lake City

10:30 am

COFFEE BREAK

10:45 am

WHEN TO REFER THE SUBSTANCE ABUSER
Panel Participants:
JOHN N. CHAPPEL, MD
ROD GWALTNEY
EILEEN R. OCHSE
BRUCE WOOLLEY, PhD

QUESTIONS AND ANSWERS

11:30 am

FETAL ALCOHOL SYNDROME
STEVEN D. MINTON, MD
Provo, Utah

(Continued on Next Page)

Wednesday (continued)

Course No. 4

CANCER IN WOMEN: THE REWARDS FOR EARLY DIAGNOSIS AND TREATMENT

Moderator:
GARY H. JOHNSON, MD
Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

1:30 pm
CANCER OF THE BREAST
HARMON J. EYRE, MD
Associate Professor
Internal Medicine and Oncology
University of Utah College of Medicine
Salt Lake City

2:10 pm
CANCER OF THE ENDOMETRIUM
W. GARY SMITH, MD
Assistant Professor
Department of Obstetrics and Gynecology
Uniiversity of Utah College of Medicine
Salt Lake City

2:50 pm
COFFEE BREAK

3:00 pm
CANCER OF THE CERVIX AND OVARY
GARY H. JOHNSON, MD
Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

3:40 pm
PANEL DISCUSSION

Course No. 5

ADVANCES IN ENDOCRINOLOGY AND METABOLISM FOR CLINICIANS

Moderator:
ALAN R. NELSON, MD
Associate Clinical Professor of Medicine
University of Utah College of Medicine
Salt Lake City

2:00 pm
ABNORMALITIES OF PHOSPHATE AND MAGNESIUM: What They Mean and What to Do About Them
DON H. NELSON, MD
Professor of Medicine
Head, Division of Endocrinology and Metabolism
University of Utah College of Medicine
Salt Lake City

HIRSUTISM AND AMENORRHEA: A Practical Approach to Diagnosis and Management
RICHARD J. WORLEY, MD
Head, Division of Endocrinology and Infertility
Associate Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

ELEVATED BLOOD LIPIDS: Changing Concepts of Significance and Treatment
DANA E. WILSON, MD
Associate Professor of Medicine
Division of Endocrinology and Metabolism
University of Utah College of Medicine
Salt Lake City

PORTABLE INSULIN INFUSION SYSTEMS AND OTHER NEW IDEAS REGARDING DIABETUS MELLITUS
RICHARD B. CANNON, MD
Endocrinologist
Salt Lake City

HORMONE-PRODUCING PITUITARY TUMORS: Clinical Presentations and Management
THEODORE S. ROBERTS, MD
Professor, Department of Surgery
University of Utah College of Medicine
Salt Lake City

Wednesday (continued)

Course No. 6

OTOLARYNGOLOGY/HEAD AND NECK SURGERY UPDATE

Moderator:
JAMES L. PARKIN, MD
Professor and Chairman
Division of Otolaryngology
University of Utah College of Medicine
Salt Lake City

2:00 pm
NEW DIAGNOSTIC TESTS IN AUDIOLOGY, INCLUDING EVOKED RESPONSE AUDIOMETRY—THE PRESCRIPTION OF HEARING AIDS
GEARY A. McCANDLESS, PhD
Professor and Head
Audiology, Division of Otolaryngology
University of Utah College of Medicine
Salt Lake City

2:40 pm
THE CHANGING BACTERIOLOGY OF OTITIS MEDIA AND SINUSITIS—ANTIBIOTIC USE IN ENT
LELAND P. JOHNSON, MD
Assistant Professor, Division of Otolaryngology
University of Utah College of Medicine
Salt Lake City

3:20 pm
COFFEE BREAK

3:30 pm
THE APPLICATIONS OF THE LASER IN HEAD AND NECK SURGERY—THE ADVANCEMENTS IN THE MANAGEMENT OF HEAD AND NECK CANCER
JAMES L. PARKIN, MD
University of Utah College of Medicine
Salt Lake City

THURSDAY, SEPTEMBER 10

Course No. 7

SPORTS MEDICINE

Moderator:
JOHN N. HENRIE, MD
Team Physician
University of Utah
Salt Lake City

8:30 am
Introduction by DR. JOHN N. HENRIE
THE RUNNER AND HIS PROBLEM
CRAIG H. McQUEEN, MD
Team Physician
University of Utah
Salt Lake City

EVALUATION OF THE ATHLETE FOR SPORTS
EARL A. LLOYD, MD
Pediatrician and Team Physician
Salt Lake City

THE DUTIES AND NEED FOR ATHLETIC TRAINERS
BILL G. BEAN, AT, C
Head Athletic Trainer
University of Utah Athletic Department
Salt Lake City

COFFEE BREAK

INJURIES OF THE BACK AND NECK
DAVID CURTIS, MD
Orthopedic Surgeon
Salt Lake City

THE SWIMMING ATHLETE
DON REDDISH, PhD
Swimming Coach and Assistant Athletic Director
University of Utah
Salt Lake City

SPECIFICITY OF EXERCISE AND TRAINING
ROBERT O. RUHLING, PhD, FACSM
Professor and Director
Human Performance Research Laboratory
University of Utah
Salt Lake City

PANEL DISCUSSION

Course No. 8

UPDATE ON SEXUAL PROBLEMS

Moderator:
WILLIAM R. KEYE, MD
Assistant Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

Thursday (continued)

9:00 am
TEENAGE SEXUAL AND SOCIAL PROBLEMS
PETER C. VAN DYCK, MD
Director, Family Health Services
Utah Department of Health
Salt Lake City

9:40 am
THE OFFICE MANAGEMENT OF COMMON SEXU PROBLEMS
WILLIAM R. KEYE, MD
University of Utah College of Medicine
Salt Lake City

10:20 am
COFFEE BREAK

10:30 am
CURRENT CONCEPTS OF SEXUAL AND MARRI COUNSELING: Office Approach
MORTON A. STENCHEVER, MD
Chairman, Department of Obstetrics and Gynecolo
University of Washington School of Medicine
Seattle
and
DIANE H. STENCHEVER, MSW
Group Counselor
Divorce Lifeline
Seattle

12:15 pm
FOURTH ANNUAL SKAGGS LUNCHEON
Empire Room, Hotel Utah

Guest Speaker:
MORTON A. STENCHEVER, MD
Seattle

Topic:
UPDATE ON DES-EXPOSED PATIENTS

2:00 pm

MENSTRUAL DISORDERS

Moderator:
E. REED HEYWOOD, MD
Chief, Division of Obstetrics
LDS Hospital
Salt Lake City

DYSFUNCTIONAL UTERINE BLEEDING
RICHARD J. WORLEY, MD
Associate Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

DYSMENORRHEA
RONALD M. LARKIN, MD
Fellow, Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

EFFECTS OF EXERCISE ON MENSTRUATION
E. REED HEYWOOD, MD
Salt Lake City

Course No. 9

THE IDENTIFICATION, STABILIZATION, AND TRANSPORT OF THE HIGH-RISK NEWBORN

Co-Moderators:
GEORGE H. DURHAM II, MD
Pediatrician
Salt Lake City
and
CARL L. BOSE, MD
Director of Transport Services
Intermountain Newborn Intensive Care Center
Salt Lake City

8:30 am
INTRODUCTION
DR. GEORGE H. DURHAM II and DR. CARL L. BO

8:40 am
REVIEW OF TRANSPORT EXPERIENCES TO PRIMARY CHILDREN'S MEDICAL CENTER—A NEONATOLOGY PERSPECTIVE
THOMAS R. HARRIS, MD
Director, Newborn Intensive Care Center
Primary Children's Medical Center
Salt Lake City

ay (continued)

ANT WITH CONGENITAL HEART DISEASE
. ORSMOND, MD
Professor
of Pediatric Cardiology
y of Utah College of Medicine
City

n
BREAK

n
N SURGICAL EMERGENCIES
JOHNSON, MD
diatric Surgery
Children's Medical Center
City

n
ANT WITH MULTIPLE CONGENITAL
MATIONS
CAREY, MD
of Genetics
y of Utah College of Medicine
City

n
ISCUSSION: QUESTIONS AND ANSWERS

No. 10
OGY: NEW DEVELOPMENTS
80'S
or:
OBERT ELTRINGHAM, MD
of Radiation Oncology
y of Utah College of Medicine
City

NTERFERON IN CANCER THERAPY
CHARLES MERIGAN, JR, MD
of Medicine
vision of Infectious Diseases
University School of Medicine
California

HYPERTHERMIA IN CLINICAL ONCOLOGY
C A. GIBBS, JR, MD
Professor
of Radiation Oncology
y of Utah College of Medicine
City

MENT OF EARLY BREAST CANCER
ADIATION THERAPY
T. SAUSE, MD
Radiation Center
pital
City

N AND ANSWER PERIOD

BREAK

ARCINOMA OF THE PROSTATE IN UTAH
ISCUSSION:
or:
OBERT ELTRINGHAM, MD
City

OLOGY
L. LYON, MD
vision of Epidemiology
y of Utah College of Medicine
City

S (Familial)
E MEIKLE, MD
e Professor
ent of Internal Medicine
y of Utah College of Medicine
City

Thursday (continued)

DETECTION
RICHARD G. MIDDLETON, MD
Professor, Department of Surgery
(Urology)
University of Utah College of Medicine
Salt Lake City

4:15 pm
QUESTION AND ANSWER PERIOD

Course No. 11

NEW INFECTIOUS DISEASES AND ANTIBIOTICS

Moderator:
CHARLES B. SMITH, MD
Professor of Medicine
Chief, Medical Service
Salt Lake Veterans Administration Hospital
and
University of Utah College of Medicine
Salt Lake City

2:00 pm
NEW ANTIBIOTICS
MERLE A. SANDE, MD
Chief of Medical Services
San Francisco General Hospital
San Francisco

3:00 pm
COFFEE BREAK

3:15 pm
TOXIC SHOCK SYNDROME
CHARLES B. SMITH, MD
Salt Lake City

4:00 pm
NEW BACTERIAL AND VIRAL CAUSES OF DIARRHEA
JAMES C. OVERALL, MD
Professor of Pediatrics
Chief, Division of Pediatric Infectious Diseases
University of Utah College of Medicine
Salt Lake City
and
WILLIS MANFORD GOOCH, MD
Clinical Associate Professor of Pediatric and Pathology
Primary Children's Center
Salt Lake City

FRIDAY, SEPTEMBER 11

Course No. 12

RECENT GASTROINTESTINAL ADVANCES

Moderator:
MALCOLM M. BERENSON, MD
Associate Professor of Medicine
Acting Chairman
Division of Gastroenterology
University of Utah College of Medicine
Salt Lake City

9:00 am
PANEL DISCUSSION #1
PEPTIC ULCER DISEASE: ISSUES AND CONTROVERSIES IN MANAGEMENT

PATHOGENETICS OF PEPTIC ULCER DISEASE
RANDALL W. BURT, MD
Assistant Professor of Medicine
University of Utah College of Medicine
Salt Lake City

MEDICAL MANAGEMENT OF PEPTIC ULCER
DOUGLAS L. ROLLINS, MD
Assistant Professor of Medicine
Medical Director
Intermountain Regional Poison Control Center
University of Utah College of Medicine
Salt Lake City

TAILORING OF SURGERY FOR ULCER DISEASE
EDWARD W. NELSON, MD
Assistant Professor of Surgery
University of Utah College of Medicine
Salt Lake City

COFFEE BREAK

Friday (continued)

PANEL DISCUSSION #2
HEPATITIS: ADVANCES IN DIAGNOSIS AND MANAGEMENT

DIAGNOSIS OF HEPATITIS
MALCOLM M. BERENSON, MD
University of Utah College of Medicine
Salt Lake City

IMMUNOTHERAPY OF HEPATITIS
DENNIS L. AVNER, MD
Assistant Professor of Medicine
University of Utah College of Medicine
Salt Lake City

MANAGEMENT OF CHRONIC ACTIVE HEPATITIS
KEITH G. TOLMAN, MD
Associate Professor
Department of Internal Medicine
University of Utah College of Medicine
Salt Lake City

Course No. 13

UPDATE IN HYPERTENSION

Moderator:
H. ALLAN BLOOMER, MD
Private Practice of Nephrology
Salt Lake City

9:00 am
The first portion of the seminar will be directed to short lectures on the recognition, evaluation and treatment of hypertension in an office setting:

EVALUATION OF THE HYPERTENSIVE PATIENT
RICHARD G. LAMBERT, MD
Private Practice of Nephrology
Salt Lake City

DRUG TREATMENT OF HYPERTENSION
H. ALLAN BLOOMER, MD
Salt Lake City

SIDE EFFECTS OF THERAPY
RICHARD G. LAMBERT, MD
Salt Lake City

RESISTANT HYPERTENSION
H. ALLAN BLOOMER, MD
Salt Lake City

HYPERTENSION IN CHILDREN AND ADOLESCENTS
RICHARD L. SIEGLER, MD
Associate Professor of Pediatrics
University of Utah College of Medicine
Salt Lake City

10:30 am
COFFEE BREAK

10:45 am
The audience will break up into three groups, each with a group leader, to discuss the management of individual cases of hypertension.
A syllabus will be provided each attendee.

Course No. 14

FAMILY PRACTICE WORKSHOP: CLINICAL TIPS FOR THE FAMILY PRACTITIONER

Moderator:
ROLF K. NALEY, MD
General Practice
Salt Lake City

9:00 am
COMMON PSYCHIATRIC PROBLEMS
DAVID R. WOOD, MD
Psychiatric Consultant
Salt Lake Community Mental Health Center
Salt Lake City

10:00 am
PLASTIC AND HAND SURGERY IN THE OFFICE
LARRY PATTON, MD
Salt Lake City

11:00 am
CHEST RADIOLOGY: Clinical Cases
IRENE M. TOCINO, MD
Department of Radiology
Veterans Administration Hospital
Salt Lake City

ther information about the scientific program contact:
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Washington State Medical Association

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Special Socioeconomic Sessions

Friday September 25, 11:00 am

- VICTOR R. FUCHS, PhD
  National Bureau of Economic Research, Stanford, California

Saturday September 26, 2:00 pm

- DANIEL C. MAGUIRE, STD
  Department of Theology, Marquette University, Milwaukee, Wisconsin

Guest Speakers

WILLIS C. MADDREY, MD
Professor of Medicine and Associate Director, Department of Medicine Johns Hopkins University, Baltimore

- **Ascites Management, Lavene Shunts, Portal Shunting and Indications for Liver Biopsy**
- **Medical Approach to Hepatobiliary**
- **Treatment of Liver and Biliary Disease by Utilizing the Percutanuous Transhepatic Approach**

MICHAEL P. FEDERLE, MD
Assistant Professor of Radiology School of Medicine, University of California, San Francisco San Francisco General Hospital

- **Air Contrast Radiography**
- **Radiographic Approach to Hepatobiliary Disease**
- **Status of Computerized Tomography**

DAVID J. CULLEN, MD
Associate Professor of Anesthesiology Harvard Medical School Director of Recovery Room—Acute Care Unit Massachusetts General Hospital, Boston

- **Results, Cost and Benefits of Intensive Care for Critically Ill Patients**

WILLIAM J. ROGERS, MD
Assistant Professor of Medicine University of Alabama, Birmingham

- **Cardiology Update on New and Effective Treatment**
- **Treatment of Unstable Angina**

GARY YATES, MA
Administrator, Comprehensive Adolescent Program Los Angeles

- **Multi-Faceted Motivations of Adolescent Behavior**
- **Barriers to Communications with Young People and Strategies for Removing Them**

DELOS M. COSGROVE, MD
Thoracic and Cardiovascular Surgeon Cleveland Clinic, Cleveland

- **Long-Term Results Following Coronary Bypass Surgery**
- **Blood Conservation in Surgery . . . Movie of Techniques**

GREGORY D. MAY, PhD
Assistant Clinical Professor Department of Family Practice School of Medicine, University of California, Davis

- **How to Enjoy the Difficult Patient**

MARIANNE E. FELICE, MD
Director, Division of Adolescent Medicine University of California Medical Center, San Diego

- **Adolescent Sexuality**
- **Special Problems of Pregnancy in Adolescents**

DALE N. GERDING, MD
Professor of Medicine, University of Minnesota Chief, Infectious Disease Section Veterans Administration Hospital, Minneapolis

- **Cephalosporins: Use and Cost Effectiveness**
- **Upper and Lower Respiratory Infections**

SCIENTIFIC SESSIONS

- EMERGENCY MEDICINE
- FAMILY PRACTICE
- INTERNAL MEDICINE
- OB/PEDIATRICS
- OPHTHALMOLOGY
- PSYCHIATRY
- SURGERY

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(206) 623-4801

in memoriam

California Medical Association

ATTWOOD, CYRIL J., Oakland. Died May 28, 1981, in Oakland, aged 75. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Dr. Attwood was a retired member of the Alameda-Contra Costa Medical Association.

CAMPISI, SALVADORE VINCENT, San Jose. Died June 4, 1981, in San Jose, aged 76. Graduate of the Creighton University School of Medicine, Omaha, 1931. Licensed in California in 1931. Dr. Campisi was a retired member of the Santa Clara County Medical Society.

COBLENTZ, DAVID R., Thousand Oaks. Died May 23, 1981, in Westlake Village, aged 43. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1963. Licensed in California in 1964. Dr. Coblentz was a member of the Ventura County Medical Society.

COLEMAN, RALPH L., San Diego. Died May 19, 1981, aged 68. Graduate of the University of Southern California School of Medicine, Los Angeles, 1941. Licensed in California in 1941. Dr. Coleman was a member of the San Diego County Medical Society.

COX, FRANCIS J., San Francisco. Died May 30, 1981, in San Francisco of cancer, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Cox was a member of the San Francisco Medical Society.

KERNS, CLAUDE L., Pittsburg. Died April 9, 1981, aged 77. Graduate of the University of Louisville School of Medicine, 1929. Licensed in California in 1930. Dr. Kerns was a retired member of the Alameda-Contra Costa Medical Association.

MAY, JAMES A., San Diego. Died May 17, 1981, in San Diego, aged 81. Graduate of the University of Minnesota Medical School, Minneapolis, 1925. Licensed in California in 1930. Dr. May was a retired member of the San Diego County Medical Society.

MCLELLAN, LAWRENCE LUMSDEN, Santa Barbara. Died May 21, 1981, in Santa Barbara of cerebrovascular accident, aged 79. Graduate of Northwestern University Medical School, Chicago, 1927. Licensed in California in 1969. Dr. McLellan was a retired member of the Medical Society of Santa Barbara County.

MUSGRAVE, PAUL J., Barstow. Died May 30, 1981, of myocardial infarct, aged 61. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1954. Licensed in California in 1955. Dr. Musgrave was a member of the San Bernardino County Medical Society.

REIS, JOSEPH BERNARD, Oakland. Died March 19, 1981, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Dr. Reis was a retired member of the Alameda-Contra Costa Medical Association.

SAINT, JAMES HAROLD, Santa Barbara. Died in May 1981 in Santa Barbara County, aged 82. Graduate of King's College, University of Durham, England, 1924. Licensed in California in 1938. Dr. Saint was a retired member of the Medical Society of Santa Barbara County.

SCHNEIDER, SHIRLEY, San Diego. Died May 17, 1981, aged 58. Graduate of the Womens Medical College of Pennsylvania, Philadelphia, 1952. Licensed in California in 1954. Dr. Schneider was a retired member of the Orange County Medical Association.

SMITH, SEYMOUR P., San Francisco. Died May 28, 1981, in San Francisco, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1934. Dr. Smith was a member of the San Francisco Medical Society.

YOUNG, JOHN D., Benicia. Died May 23, 1981, aged 73. Graduate of the University of Louisville School of Medicine, 1935. Licensed in California in 1945. Dr. Young was a member of the Alameda-Contra Costa Medical Association.

Utah State Medical Association

MAW, RAYMOND BROWN, Salt Lake City. Died May 10, 1981, in Salt Lake City, aged 86. Graduate of the University of Louisville School of Medicine, 1926. Licensed in Utah in 1937. Dr. Maw was a member of the Salt Lake County Medical Society.

Washington State Medical Association

AYLEN, CHARLES H., Puyallup. Died April 18, 1981, in Puyallup, aged 91. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1915. Licensed in Washington in 1920. Dr. Aylen was a retired member of the Pierce County Medical Society.

DEROETTH, ANDREW F. M., Spokane. Died May 13, 1981, in Spokane, aged 87. Graduate of the University of Medical Sciences School of Medicine, Budapest, 1919. Licensed in Washington in 1939. Dr. deRoetth was a retired member of the Spokane County Medical Society.

MOSIMAN, ROSCOE E., Seattle. Died May 17, 1981, in Seattle, aged 95. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1914. Licensed in Washington in 1919. Dr. Mosiman was a retired member of the King County Medical Society.

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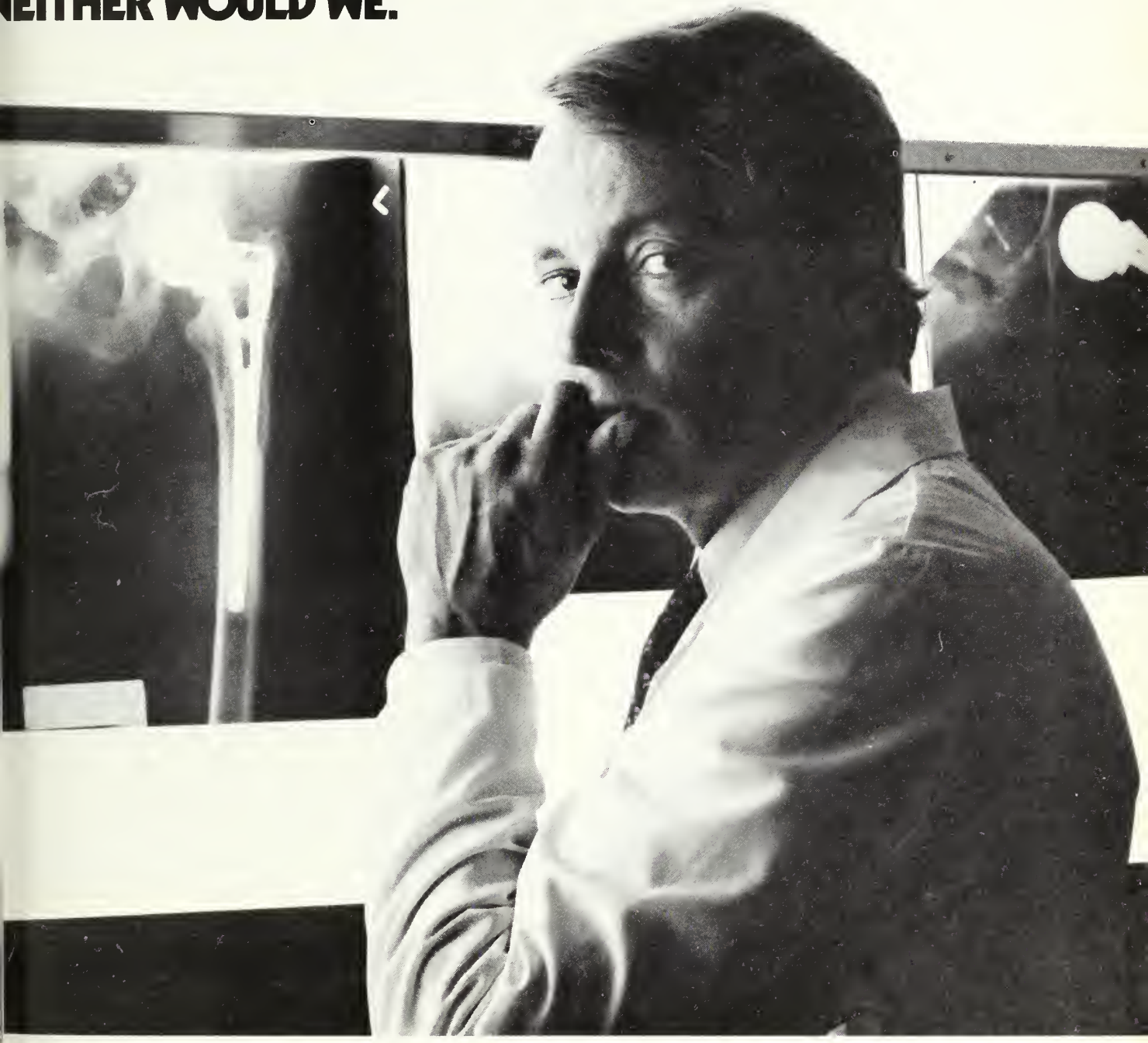

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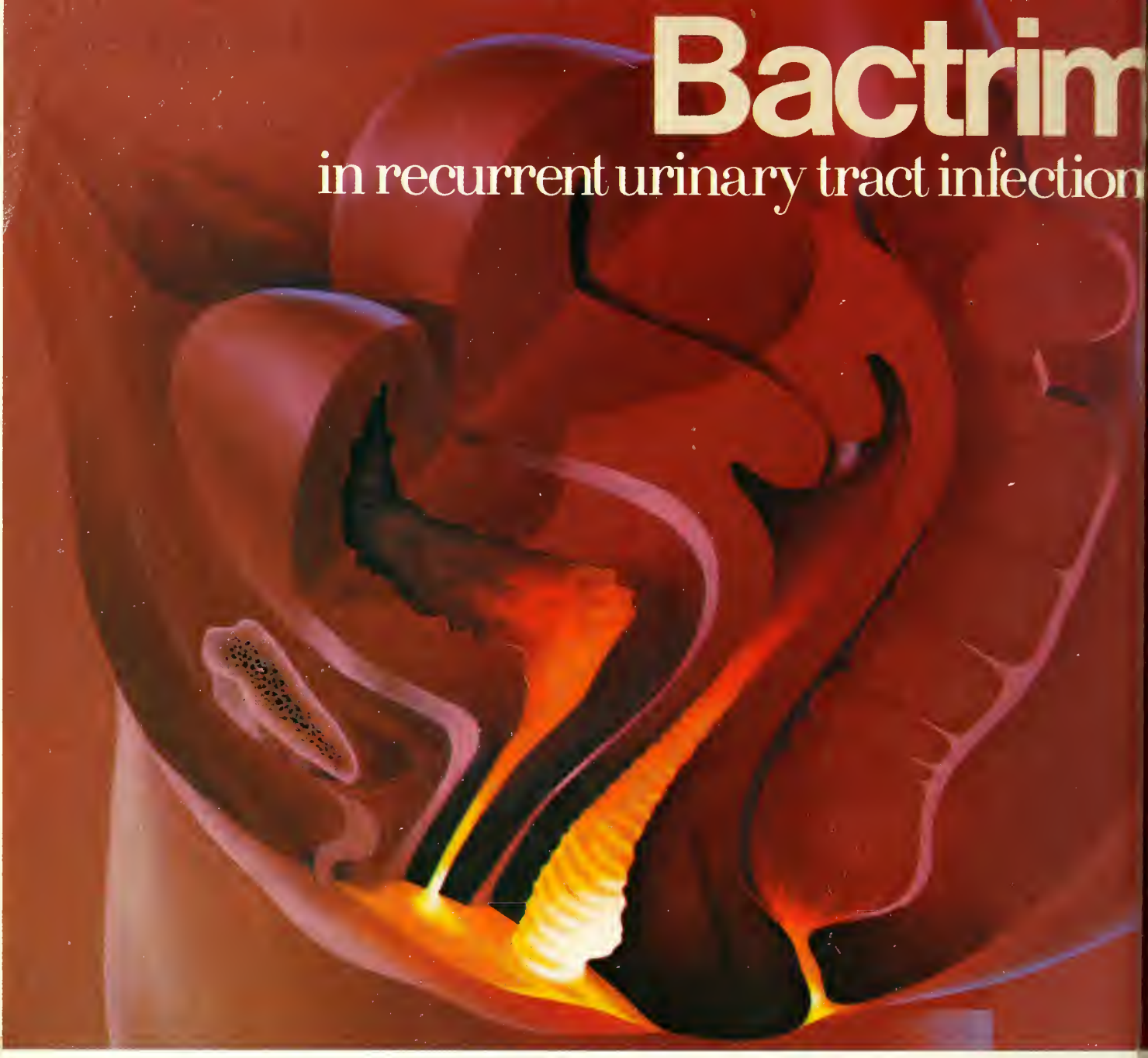

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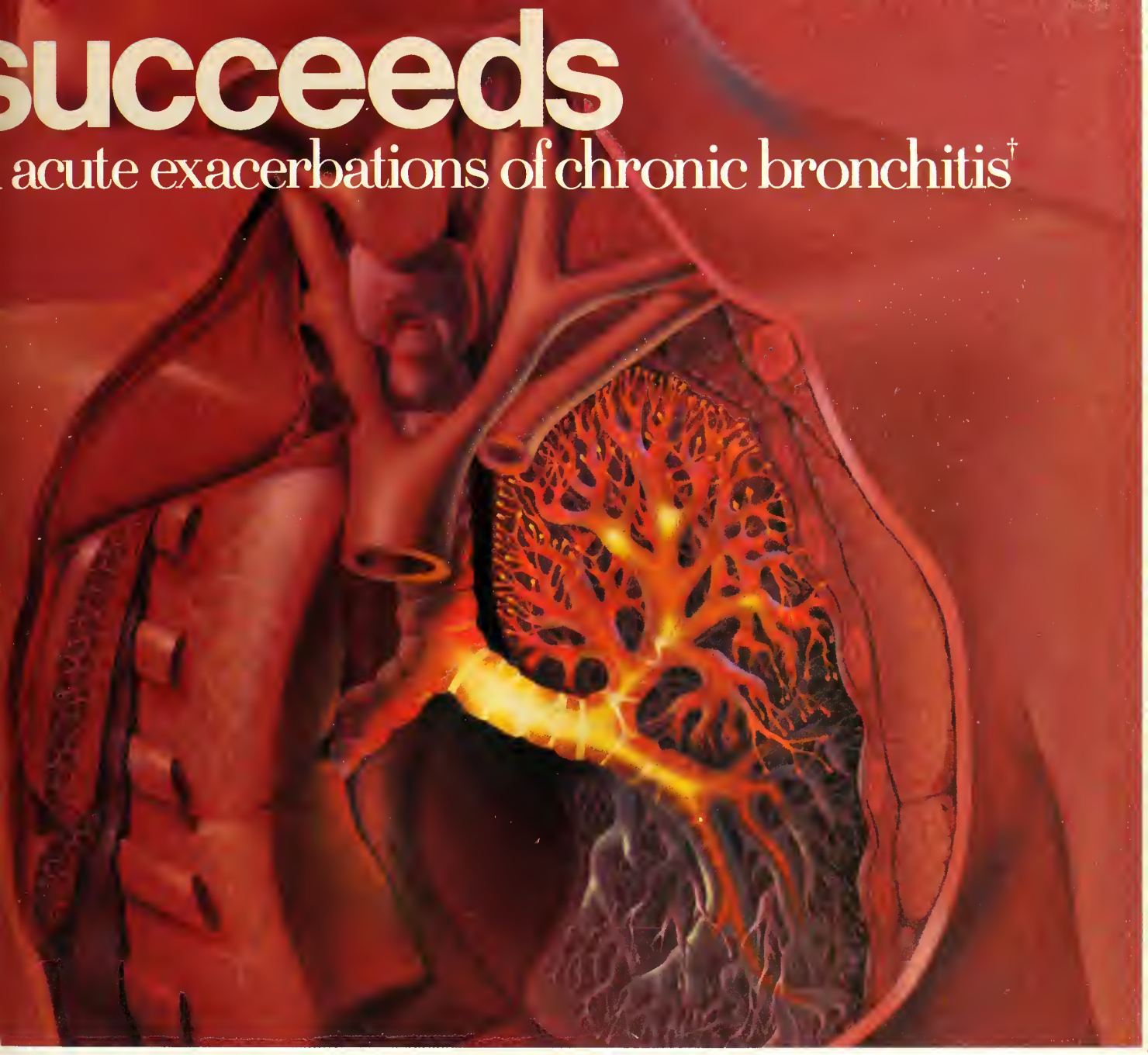
*Due to susceptible strains of indicated organ

succeeds

acute exacerbations of chronic bronchitis†



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susceptible strains of
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ome advantage over the
a single antimicrobial

n RH, Swartz MH N Engl J
3 426-432, Aug 21, 1980
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In controlled multicenter studies involving *H. influenzae* and *S. pneumoniae*, a 7-day follow-up after 14-day treatment showed the causative organisms were eliminated in 50 of 55 patients (91%).[2] Five patients did not return for follow-up.

During therapy, maintain adequate fluid intake. Bactrim is contraindicated during pregnancy at term and lactation, in patients hypersensitive to its components, and in infants less than two months of age.

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see next page for summary of product information.

Bactrim™ DS

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Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.
Note The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides, patients with documented megaloblastic anemia due to folate deficiency, pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus, infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended, therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin, reassess coagulation time when administering Bactrim to these patients. *Pregnancy* Teratogenic Effects. Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN
Adults Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.
Children Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.
For patients with renal impairment Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:
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OB/GYN: Board Certified/Eligible—To join 30 Phys. Multispecialty Group in Central California. City of 50,000—Service area approx. 300,000. Early partnership/stockholder with **no** initial investment. Full clinic facilities 7 years old. Excellent Family/Recreational area. Contact James Simpson, MD, Visalia Medical Clinic, 5400 W. Hillsdale, Visalia, CA 93291.

KING CITY, MONTEREY COUNTY, CALIFORNIA: "STEINBECK COUNTRY"—8-man multispecialty group is looking for 2 Family Practitioners-FP's must be willing to take OB's. Ability to speak Spanish helpful but not mandatory. King City is located 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, 1st year guaranteed minimum salary, opportunity to join corporation after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Admin. SoMoCo Medical Group, 210 Canal St., King City, CA 93930, or telephone (408) 385-5471.

INTERNIST—Wanted to affiliate with one FP and one internist in practices located here total 10 years. Small town in Northern California redwood region is prime location. Inquire and send CV to R. A. Reisman, MD, Smalley Medical Center, Willits, CA 95490.

Part-Time Medical Consultant Contract

Physicians needed to work under contract for the Social Security Administration's Disability Insurance Program in: Internal Medicine, Orthopedics, Rheumatology, Cardiology, Neurology and Psychiatry. Involves review of medical evidence in disability claims at 100 Van Ness Ave., San Francisco, CA. No patient contact. Selection criteria include acceptable training in medical specialty leading to Board eligibility or certification; clinical practice experience necessary, current and ongoing clinical practice preferred; availability between 7:30 a.m. and 5:30 p.m.; valid license to practice medicine in a State in this country. Previous claims review or review of medical evidence and interpretation of regulations desirable but not mandatory. Send curriculum vitae and availability information to:

Contracting Officer, Department of Health and Human Services, Room 8, 50 United Nations Plaza, San Francisco, CA 94102.

CV's received after 8/14 accepted only if there are too few timely responses.

PHYSICIANS WANTED

SURGEON & FP NEEDED: Multispecialty Clinic (Surgeons, Internists, FP's) in rural, mountainous area of northern Idaho is looking for a General Surgeon and a Family Practice physician. Contact Dr. Fitz (208) 784-1141.

GENERAL SURGEON: Bd elg./cert. needed by 8-man multispecialty Group in King City, Monterey County, California, "Steinbeck Country." King City is 1 hr. from Monterey Peninsula and 3 hrs. from San Francisco. Excellent fringe benefits, opportunity to join Corp. after 6-12 months. Send CV or contact: Allan L. Fisher, MD, or Lee S. Roberts, Administrator, at Southern Monterey County Medical Group (A professional Corporation), 210 Canal St., King City, CA 93930, (408) 385-5471.

PSYCHIATRIST WANTED: Very active private practice in Santa Barbara need Psychiatrist. Position open in Summer or Fall of 81. Interested persons please contact Bob Hyman, MD, at (805) 964-0553.

WANTED: Internist to join two busy internists and two physicians assistants in a practice with a strong hospital orientation. The practice has significant numbers of minority and gay patients. The emphasis is on patient care. Competitive salary, incentive, and excellent fringe benefits offered. Minority, Women, and Gay Physicians are invited to apply: Send CV to Dr. Robert Scott, 590 Radnor Road, Oakland, CA 94606 or call (415) 834-1950.

OB/GYN—multi-specialty clinic of 31 physicians offers immediate fulltime opportunity to a Board Certified or eligible OB/GYN physician with a California license. Actively seeking male or female. Shareholder status in six months. All practice costs paid. Excellent retirement program and benefits. Reply to Mr. Dale R. Molesworth, Clinic Administrator, San Luis Medical Clinic, Ltd., 1235 Osos Street, San Luis Obispo, CA 93401.

CALIFORNIA—BE/BC. Family Physician wanted for small multi-specialty group in desirable Roseville suburb of Sacramento. Combines office practice with part-time Minor Emergency Clinic. Competitive salary. Fringe; leads to partnership. Excellent hospital and office facilities. Position available immediately. Contact Judy Cook, MD, Sierra Valley Medical Group, 1101 Smith Lane, Roseville, CA 95678, (916) 969-7767.

NEBRASKA EMERGENCY MEDICINE: Directorships and clinical positions available in several moderate volume emergency departments located in the western and central portions of the state. Excellent guaranteed income, plus additional stipend for directors' duties. Professional liability insurance provided; flexible scheduling without on-call involvement. For details, forward credentials in confidence to William Salmo, Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903; or call toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981).

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(Continued on Page 31)

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ANESTHESIOLOGY

August 23-26—**Clinical Neuroanesthesia.** California Society of Anesthesiologists at UCSD. Sunday-Wednesday. 24 hrs. $325, CSA members; $375, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** See "Of Interest to All," August 29-30.

October 3-4—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

January 10-15—**Anesthesiology Update.** UCSD. Sunday-Friday.

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

September 25—**Workshop on Flexible Fiberoptic Sigmoidoscopy.** USC. Friday. 6 hrs. Contact: Katie Eisenberg, MPH, USC Comprehensive Cancer Center, Regional Activities Program, 1721 Griffin Ave., Los Angeles 90031. (213) 224-7416.

October 3—**Light on the Black Cancer.** USC. Saturday. 5½ hrs. $60.

October 9-11—**Blood Diseases and Cancer in Children.** See Pediatrics, October 9-11.

October 12-16—**Medical Oncology Review.** American College of Physicians at Princess Kaiulani Hotel, Honolulu. Monday-Friday. 38¼ hrs. Contact: ACP, 4200 Pine St., Philadelphia 19104.

October 26-28—**Fifth Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 31—**4th Annual Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joann Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

November 6—**Causes of Cancer.** Calif. Hospital Medical Center, Am. Cancer Soc., USC Cancer Management Network, at Biltmore Hotel, Los Angeles. Friday. $85. Contact: Kenneth Senter, MD, USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Phinney Hall 105, Los Angeles 90031. (213) 742-5750.

November 13-14—**Current Concepts on Cancer Management: Successful Treatment and Its Consequences.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $150, before Sept. 15; $200, thereafter. Contact: Office of Cont. Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

EMERGENCY MEDICINE

September 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

October 2-3—**Symposium on Medical Emergencies.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

October 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

November 23-24—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

MEDICINE

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** See Psychiatry, August 15-21.

August 21-22—**Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

August 25-June 29—**Seminars in Nephrology.** USC at Holiday Inn, Los Angeles/Westwood. Tuesday evenings; five sessions. 12½ hrs. $70.

September 5-8—**Advances in Internal Medicine.** UCSD. Saturday-Tuesday.

September 5-9—**Dermatopathology.** UCD at Silverado Country Club, Napa. Saturday-Wednesday.

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 12-13—**Severe Asthma: State of the Art for the Specialist.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Traci Drelen, LACMA, 1925 Wilshire Blvd., Los Angeles 90057.

September 14-17—**Current Concepts, Controversies and Clinical Strategies in Gastroenterology.** Cedars-Sinai Medical Center at Beverly Hilton Hotel, Beverly Hills. Monday-Thursday. 27 hrs. $450. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., Rm. 2049, P.O. 48750, Los Angeles 90048. (213) 855-5547.

September 18—**Diabetes and the Kidney—14th Annual Symposium on Renal Disease.** National Kidney Foundation of Northern Calif. at Hilton, San Francisco. Friday. $60. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd., Burlingame 94010. (415) 697-0110.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 19—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

September 24-26—**Office Dermatology.** STAN. Thursday-Saturday. 19 hrs. $275.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 3-4—**The Skin from A to Z.** UCSF. Saturday-Sunday.

October 3-10—**Cardiology—1981.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $350.

October 6-7—**48th Annual Fall Symposium and 13th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $125, AHA member; $150, nonmember. Contact: Mary Frances Flynn, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 6-9—**Advances in Internal Medicine.** American College of Physicians at Letterman Army Institute, San Francisco. Tuesday-Friday. 22 hrs. Contact: ACP, 4200 Pine St., Philadelphia 19104.

October 7-9—**Current Neurology.** Straub Clinic and Hospital at Honolulu Art Academy, Honolulu. Wednesday-Friday. 12 hrs. $175. Contact: Office of Medical Administration, Straub Clinic and Hospital, 888 S. King St., Honolulu 96813.

October 9-10—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $50/day. Contact: Paul H. Jacobs, MD, Derm. Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 9-11—**California Society of Internal Medicine—Annual Meeting.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 10—**Clinics in Medicine—Cardiology.** PMC. Saturday. 3 hrs. $40.

October 12-16—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs.

October 14—**Thrombophlebitis and Thromboembolic Disease.** LLU. Wednesday. 4 hrs.

October 14-December 16—**Nephrology.** UCLA. Wednesday evenings.

October 15-17—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 17—**Pediatric Allergy: Principles and Management.** See Pediatrics, October 17.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 19-22—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Mark Hopkins Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

October 21—**Endocrine—Third Annual Symposium.** The Hospital of the Good Samaritan at Hyatt Regency, Los Angeles. Wednesday. 7 hrs. $75. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 24—**Allergy/Immunology.** PMC. Saturday. 6 hrs.

October 24-25—**Diabetes Workshop.** UCSF. Saturday-Sunday.

October 24-31—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

(Continued on Page 29)

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The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13.9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression[2,3a] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered

d Impaired glucose tolerance.

e Decreased pregnanediol excretion

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (*e.g.* three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

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(Continued from Page 25)

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

October 28-30—**Neurology for the Internist and Family Physician.** USC at Marriott Hotel, Newport Beach. Wednesday-Friday. 24 hrs. $250.

October 29-31—**Cardiology Update—1981.** American College of Cardiology and UCSF at Quail Lodge, Carmel Valley. Thursday-Saturday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

November 6-8—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 6-8—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 7—**Neurological Assessment.** PMC. Saturday. 6 hrs.

November 11—**Acid Base Disorders.** LLU. Wednesday.

November 14—**Clinics in Medicine—Nephrology/Hypertension.** PMC. Saturday. 3 hrs. $40.

November 14—**Modern Drug Management of Common Pulmonary Diseases.** UCSF at Fresno. Saturday. Contact: Kathleen Wolff, Area Health Education Ctr., 5110 E. Clinton Way, Suite 201, Fresno 93727. (209) 252-1948.

November 16-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** Am. College of Allergists, Sociedad Mexicana de Allergia E Immunologia, Autonoma Univ. of Baja and UCSD at San Diego (16-18) and Tijuana (19-20). Monday-Friday. 21 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

December 11-13—**Cardiology for the Primary Care Physician.** UCD. Friday-Sunday.

December 12—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

January-March—**Endocrinology for the Practicing Internist.** UCLA. Wednesday evenings.

January 9—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 20-22—**Conference on Nephrology.** UCSD at Hilton, San Diego. Wednesday-Friday.

January 28-30—**Fundamentals of Echocardiography—An Introductory Course for Clinicians.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

August 29-September 5—**Concepts in Infertility.** See Of Interest To All, August 29-September 5.

October 17—**Preventing Birth Defects.** UCD and March of Dimes at Sierra Inn, Sacramento. Contact: UCD.

October 26-30—**11th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 7-9—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 14-16—**Perinatology.** UCSD at Holiday Inn at Embarcadero, San Diego. Monday-Wednesday.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

PEDIATRICS

September 23-24—**38th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 25-29—**Pediatric Urology.** UCD at Silverado Country Club, Napa. Friday-Tuesday.

October 2-3—**Pediatric Gastroenterology and Nutrition.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 9-11—**Blood Diseases and Cancer in Children.** STAN at Children's Hospital at Stanford. Friday-Sunday.

October 17—**Pediatric Allergy: Principles and Management.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 453-8696 or (916) 486-2690.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

October 23-24—**New Directions in Care for the Handicapped Child.** State Dept. of Special Education and Northern Calif. Chap., Am. Academy of Pediatrics, at Fresno Community Hospital, Fresno. Friday-Saturday. $75. Contact: Peter Miller, MD, Marin Civic Ctr., Rm. 280, San Rafael 94903. (415) 499-6877.

October 23-24—**The Pediatrician's Role in the Management of Neurological and Neurosurgical Problems.** Children's Hospital Medical Center of Northern Calif. at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

(Continued on Page 37)

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COLORADO EMERGENCY MEDICINE: Directorship and Clinical positions available in Northeastern portion of the state in moderate volume emergency department. Hourly quarantee plus compensation for Director's added responsibilities. Paid professional liability insurance and other amenities. For further information contact William Salmo toll-free 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

WESTERN ARIZONA AND SOUTHERN NEVADA —EMERGENCY MEDICINE: Clinical and Directorship positions available in several emergency departments. Excellent compensation, paid professional liability insurance, flexible scheduling. For further details contact William Salmo toll-free at 1 (800) 525-3681 (within Colorado call collect (303) 471-4981); or send credentials in complete confidence to Chase Stone Center, Holly Sugar Building, Suite 1070, Colorado Springs, CO 80903.

CALIFORNIA, SAN JOSE: Experienced Emergency Physician with Spanish-speaking ability preferable, wanted to join our group practicing in San Jose at a University-affiliated medical center and two community hospitals. Total patient volume of 90,000; fee-for-service compensation. If interested, send CV or contact: James B. Lane, MD, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Phone (408) 293-8881.

INTERNIST, CARDIOLOGIST, PULMONARY. No state income tax. Year round pleasant living. Equal opportunity employer. Send CV to R. J. Hudson, MD, Chief of Staff, Veterans Administration Medical Center, Marlin, TX 76661.

PACIFIC NORTHWEST—Family Practitioners-4, Cardiologist, ENT Specialists-2, General Surgeon, Internists-3, Rheumatologist, Surgeon specializing in cancer surgery, Urologists-2. Clinic adjacent to modern 150 bed hospital, serving an expanding community of approximately 50,000 people. Relaxing life style, no smog or traffic congestion. Initial investment flexible. Excellent for outdoor recreation, beaches. Two major metropolitan areas, International Airports within a couple of hours freeway drive. Enclose curriculum vita with initial response. P.O. Box 574, Chehalis, WA 98532.

CALIFORNIA, SAN JOSE: Primary Care Physician with experience in minor trauma and Peds. wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Tel: (408) 293-8881.

NEW MEXICO PRIMARY CARE PRACTICE OPPORTUNITIES. Free nonprofit statewide placement service. Call 1-800-824-7888. California 1-800-852-7777, ask for operator 322. New Mexico Health Resources, Box 8735W, Albuquerque, New Mexico 87198.

PHYSICIAN—Full-Time Permanent $48,000 per year. Interfaces with an interdisciplinary team of professionals to provide diagnostic medical evaluations and related services to developmentally disabled clients. Registered valid license to practice medicine in California issued by State Board of Medical Quality Assurance. Submit vitae or résumé to: Administrative Services Officer, San Gabriel Valley Regional Center, 1373 East Center Court Drive, Covina, CA 91724. Equal Opportunity Employer.

FAMILY PRACTITIONER NEEDED. Rural town in Scenic Eastern Idaho near Yellowstone with established modern Hospital and Clinic. Has immediate/opening available for one General-Family Practitioner. Competitive Salary, fringe benefits and incentive bonus. Write or call H. Bergman, Administrator, Ashton Memorial Hospital, Ashton, Idaho 83420; (208) 652-7461.

ORTHOPEDIC SURGEON

. . . sought for Palm Springs Medical Center, a thirty physician multispecialty group practice located in beautiful Palm Springs, Californa. Must be board certified with minimum three years in practice. First year salary negotiable with option for full financial participation after 9-12 months. Excellent benefits plus qualified profit-sharing plan.

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INTERNAL MEDICINE/EMERGENCY ROOM—Rural part-time private practice with three other Internists 50 miles north of Sacramento, working four shifts per month, flexibly scheduled, approximately 50 hours each. Allows you to live in rural town or Bay area. Acute medicine and E.R. coverage. Must be board eligible in medicine. Salary $4,000/month with future partnership. Sense of humor preferred. Contact: Charles Rath, MD, 199 E. Webster, Colusa, CA; (916) 458-7739.

TEXAS EMERGENCY MEDICINE: Clinical positions available in moderate volume emergency department located in El Paso. Competitive hourly guarantee plus bonus based on productivity. Flexible scheduling; paid professional liability insurance provided. For details, send credentials in confidence to Sue Haberman, 845 East Arapaho, Suite A-1, Richardson, TX 75081; or call collect (214) 669-0606.

INTERNISTS NEEDED both solo and group practices in Kennewick, Washington. Call collect —Raymond Kerr, MD; (509) 582-5137.

NUCLEAR MEDICINE, Diagnostic Ultrasound Physician (ABNM), to join one fulltime physician in multihospital and office practice in California. Significant experience in cardiac nuclear medicine and "hands on" talent in diagnostic ultrasound required. Reply: Stephen J. Bruny, MD, Nuclear Associates Medical Group, 3526 East Shields, Fresno, CA 93726.

DEVELOPMENTAL DISABILITIES PROGRAMS

Opportunities are available for internists, family practitioners and psychiatrists to work with developmentally disabled people in State residential communities. Locations from Los Angeles to northern California. Challenging and varied cases, congenial professional environment, excellent civil service benefits.

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COALINGA, CALIFORNIA: Rare opportunity in town of 10,000 for solo GP/FP. No night or weekend call. Guarantee, paid malpractice, profit sharing, 90 percent private patients. Contact: Carol Sweig, Western Physicians, 1124 Ballena Blvd., Alameda, CA 94501; (415) 521-4110.

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Available immediately. Send CV to Box 6222, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OREGON—Board certified Internist needed October 1981. Young, dynamic, 5 physician multispecialty group. New clinic building adjacent to hospital. Rural community located 90 minutes from Portland on Pacific Ocean. Energy and dedication required. Civic orientation a plus. Contact North Coast Medical Center PC, 727 Wahanna Road, Seaside, Oregon 97138. Phone (503) 738-9553 or 738-7405.

SITUATIONS WANTED

PATHOLOGIST, certified (AP/CP/RIP) with special interest in Clinical Chemistry and computer applications. Also certified in Nuclear Medicine. Eight years experience in Pathology and four years experience in Nuclear Medicine. Foreign graduate, US trained, California license. Box 6213, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER, age 36, currently in private practice in midwest, wants to move back to salt-water community on west coast (licensed California, Washington). I do general medicine, minor surgery, peds, house calls; am chairman of hospital FP/GP department and on the Preventive Medicine faculty at medical school. Have training in group therapy and emphasize patient education and comprehensive humanistic care in my practice. Looking for community, associate, or office space. Need to spend more time with family: artist/therapist wife and preschool children. Am teacher of TM technique and student of alternative healing. Box 6214, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FOR RURAL OR NON-METROPOLITAN HOSPITAL OR MEDICAL GROUP experienced PHYSIATRIST is available to establish or enhance Physical Medicine and Rehabilitation Dept. Competent in Orthopaedic Medicine, PM&R, including EMG's, and Sports Medicine. Box 6216, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL SURGEON University trained, Board Certified. FACS, licensed in California, Washington State, Illinois. Prefer Trauma and Critical Care management type practice. Résumé available. Reply, Box 6209, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ORTHOPEDIC SURGEON. Age 69. Board certified. Interested in office orthopedics and/or disability examinations. Apply Box 6225, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SOUTH BAY INTERNIST (ABIM) with family, desires job-sharing or part-time (to 70 percent) private association. Will consider relocation within California. Contact Box 6223, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, 36, certified AP-CP, also BC Internal medicine/experienced, seeks challenging position western states. Box 6225, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 33)

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Other topics such as movement disorders, visual problems as a sign of neurologic disease, problems in dementia, seizures, particularly the use of newer drugs, neurologic presentation of medical disease and recent developments in multiple sclerosis and amyotrophic lateral sclerosis will be presented.

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FOR FURTHER INFORMATION CONTACT: Associate Dean, USC School of Medicine, Postgraduate Division, KAM 318, 2025 Zonal Avenue, Los Angeles, CA 90033; (213) 224-7051.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 4, 1981—Editor: W. Maxwell Cowan, Washington University School of Medicine; Associate Editors: Zach W. Hall, University of California, San Francisco, and Eric R. Kandel, College of Physicians and Surgeons of Columbia University. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1981. 556 pages, $20.00 (U.S.A.), $21.00 (elsewhere).

ARE YOU LISTENING, DOCTOR?—Albert Schrut, MD, In private practice, adult and child psychiatry and psychoanalysis, Los Angeles. Nelson-Hall Inc., Publishers, 111 North Canal Street, Chicago (60606), 1980. 232 pages, $15.95.

BASIC CLINICAL PHARMACOKINETICS—Michael E. Winter, PharmD, Associate Clinical Professor of Pharmacy, School of Pharmacy, University of California, San Francisco, and Co-Director, Clinical Pharmacokinetics Laboratory, University of California Hospitals and Clinics, San Francisco; and Brian S. Katcher, PharmD, Lecturer in Pharmacy; Mary Anne Koda-Kimble, PharmD, Associate Clinical Professor of Pharmacy, Vice Chairwoman, Division of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco. Applied Therapeutics, Inc., P.O. Box 31-747, San Francisco, 1980. 231 pages, $22.00.

BONE METASTASIS—Volume Five in the series: METASTASIS—Edited by Leonard Weiss, ScD, MD, PhD, Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York; and Harvey A. Gilbert, MD, Department of Radiation Therapy, Southern California Permanente Medical Group, Los Angeles. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 512 pages, $55.00.

CLINICAL DIAGNOSTIC MANUAL FOR THE HOUSE OFFICER—Edited by Kenneth L. Baughman, MD, Assistant Professor, Department of Medicine, The Johns Hopkins Hospital, Baltimore; and Bruce M. Greene, MD, Assistant Professor, Department of Medicine, Case Western Reserve University, University Hospitals, Cleveland. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1981. 159 pages, $9.95 (paperback).

THE COMPREHENSIVE HANDBOOK OF BEHAVIORAL MEDICINE—Edited by James M. Ferguson, MD, Medical Director, Gifford Mental Health Center, Assistant Professor of Psychiatry, University of California, San Diego, School of Medicine and Department of Psychiatry, VA Medical Center, La Jolla; and C. Barr Taylor, MD, Assistant Professor of Psychiatry, Stanford University Medical Center, Stanford. Volume 1: SYSTEMS INTERVENTION, 304 pages, 1980; Volume 2: SYNDROMES & SPECIAL AREAS, 350 pages, 1981, $30.00; Volume 3: EXTENDED APPLICATIONS & ISSUES, 344 pages, 1980, $30.00. SP Medical & Scientific Books, 175-20 Wexford Terrace, Jamaica, NY 11432.

CURRENT PSYCHIATRIC THERAPIES—VOLUME 19—Edited by Jules H. Masserman, MD, Professor Emeritus of Psychiatry and Neurology, Northwestern University, Chicago. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1980. 218 pages, $29.50.

EMOTIONAL DISORDERS: An Outline Guide to Diagnosis and Pharmacological Treatment—Third Edition—Albert DiMascio, PhD, at the time of his death, Director of Psychopharmacology, Department of Mental Health, Commonwealth of Massachusetts; and Harold L. Goldberg, MD, Clinical Professor in Psychiatry, Tufts University School of Medicine, and Director, West-Ros-Park Mental Health Center, Boston. Medical Economics Books, (DPRKO), Box 157, Florence, KY (41042), 1981. 146 pages, $13.95, plus $1 handling charge.

FETAL HEART RATE MONITORING—Roger K. Freeman, MD, Medical Director, Women's Hospital, Memorial Hospital Medical Center, Long Beach, and Professor, Department of Obstetrics and Gynecology, University of California, Irvine; and Thomas J. Garite, MD, Associate Medical Director for Perinatology, Women's Hospital, Memorial Hospital Medical Center, Long Beach, and Assistant Professor, Department of Obstetrics and Gynecology, University of California, Irvine. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1981. 182 pages, $27.00.

INTRODUCTION TO ABDOMINAL SURGERY—Fifty Clinical Studies—Clarence J. Schein, MD, Professor of Surgery at Albert Einstein College of Medicine, Chief of Surgery at the Hospital of the Albert Einstein College of Medicine, and Attending Surgeon at the Montefiore Hospital and Medical Center, Bronx, New York. Harper & Row Publishers, Inc., 2350 Virginia Ave., Hagerstown, MD (21740), 1981. 521 pages, $30.00.

INTRODUCTION TO BASIC PATHOLOGY. Medical Economics Books, Box 157, Florence, KY (41042), 1980. 126 pages, $10.95.

AN INTRODUCTION TO FAMILY MEDICINE—Ian R. McWhinney, MD, MRCP, CCFP, FRCGP, Professor and Chairman, Department of Family Medicine, University of Western Ontario. Oxford University Press, 200 Madison Ave., New York City (10016), 1981. 219 pages, $16.95 (cloth), $9.95 (paperback).

ISLER'S POCKET DICTIONARY OF DIAGNOSTIC TESTS, PROCEDURES & TERMS—Charlotte Isler, RN, Clinical Editor, **RN Magazine.** Medical Economics Books, Box 157, Florence, KY (41042), 1981. 150 pages, $7.95 (softcover).

(Continued from Page 31)

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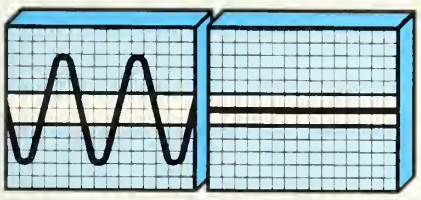

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Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

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Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

Respiratory: Tachypnea.

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Others: Hyperglycemia and inappropriate ADH syndrome.

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(Continued from Page 29)

December 4-6—**Kids Have Bones, Too.** UCD. Friday-Sunday.

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

PSYCHIATRY

August 15-21—**Neuropsychiatric Issues in the Law, Education and Medicine: Hyperactivity and Dyscontrol Syndrome.** So. Calif. Neuropsychiatric Institute and Hawaii Psychiatric Society at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 15 hrs. Contact: Gail Waldron, MD, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

August 20-22—**Practical Medicine for the General Psychiatrist.** UCSD at Hyatt Islandia, San Diego. Thursday-Saturday.

September 11-12—**The Family in Therapy.** The Family Institute of Berkeley at Los Angeles. Friday-Saturday. 12 hrs. $135. Contact: The Family Inst. of Berkeley, 1542 LeRoy Ave., Berkeley 94708. (415) 548-8787.

September 14-15—**The Family in Therapy.** The Family Institute of Berkeley. Berkeley. Monday-Tuesday. Contact: The Family Inst. of Berkeley, 1542 LeRoy Ave., Berkeley 94708. (415) 548-8787.

October 22-23—**Mental Health Issues of the Individual with a Developmental Disability—An Intensive Seminar on Treatment Techniques and Strategies.** Hope Rehabilitation Services and San Jose State Univ. at Rickey's Hyatt House, Palo Alto. Thursday-Friday. Contact: Bonnie Bernell or Fay Sells, HRS, 1539 Parkmoor Plaza, San Jose 95128. (408) 998-4673.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** UCD at Red Lion Inn, Sacramento. Saturday. 7¼ hrs. $75.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

RADIOLOGY AND PATHOLOGY

August 16-21—**23rd Annual Postgraduate Course in Dermal Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Newporter Inn, Newport Beach. Sunday-Friday. Contact: Program Coordinator, Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 29-September 5—**Diagnostic Radiology: An In-Depth Seminar Approach to Diagnostic Imaging.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 24 hrs. $345.

September 5-9—**Dermatopathology.** See Medicine, September 5-9.

September 13—**Introduction to Digital Radiography.** STAN. Sunday. 6 hrs.

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

September 25-26—**The Dematiaceous Fungi: Clinical and Laboratory Identification.** UCSF. Friday-Saturday. 7½ hrs. $125.

October 2—**Uroradiology Seminar.** Orange Co. Urological Soc. and Western Section, American Urological Assn., at South Coast Plaza Hotel, Costa Mesa. Friday. $100. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

October 8-9—**Fine Needle Aspiration of Breast and Thyroid.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. 13 hrs.

October 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. $100, before Sept. 15; $125, thereafter. Contact: Dr. Luis M. de la Maza, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

October 9-10—**Mycology Review.** See Medicine, October 9-10.

October 10-18—**6th Annual International Body Imaging Conference.** West Park Hospital and American College of Radiology at Hyatt Regency, Maui. 9 days. 25 hrs. $365. Contact: West Park Hosp., Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 29-30—**Laboratory Diagnosis in Clinical Practice.** UCSF. Thursday-Friday.

October 31—**GYN Pathology.** USC. Saturday. 6 hrs. $60.

November 24—**Use of Antimicrobial Agents Old and New.** UCD at Red Lion Inn, Sacramento. Tuesday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

September 9—**New Concepts in the Diagnosis and Management of Peripheral Vascular Disease.** LLU. Wednesday. 4 hrs.

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

September 25-29—**Pediatric Urology.** See Pediatrics, September 25-29.

October 2—**Medical Malpractice in Ophthalmology—A Review of Common Diagnostic and Therapeutic Errors.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. 8 hrs. $50. Contact: Margaret Frederick, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 2—**Uroradiology Seminar.** See Radiology and Pathology, October 2.

October 2-3—**Cataract Surgery and Intraocular Lenses Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

October 3-10—**3rd International Seminar on Operative Arthoscopy.** UCLA at Maui. One week.

October 9-10—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $225.

October 11-16—**American College of Surgeons—67th Annual Clinical Congress.** Fairmont and Hilton Hotels, San Francisco. Sunday-Friday. Contact: Fred C. Spillman, Convention Mgr., ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 15-17—**New Horizons in Knee and Hip Surgery.** UCLA. Thursday-Saturday.

October 16-17—**Fracture Bracing Workshops.** USC at University Hilton, Los Angeles. Friday-Saturday. 17 hrs. $375.

November 7-8—**Clinical Application of Evoked Potentials.** UCSF. Saturday-Sunday.

November 11-15—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** Institute for Medical Education and Research at Silverado County Club, Napa. Wednesday-Sunday. 20 hrs. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

November 12-14—**Techniques in Urinary Tract Surgery.** American Urological Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611.

December 2-4—**Corneal and Refractive Surgery—An Up-to-Date Evaluation.** UCSF. Wednesday-Friday.

December 3-6—**Bone Grafting: Biology and Application.** Plastic Surgery Research Foundation at Hyatt Islandia, San Diego. Thursday-Sunday. 17 hrs. $275. Contact: Jack C. Fisher, MD, P.O. Box 33387, San Diego 92103.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

January 15-16—**Vitrectomy Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Stereotactic Vitreous Microsurgery.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

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August 16-21—**9th Annual Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday. 36 hrs.

August 28-30—**Orthopedics for the Primary Care Physician.** UCLA at Newporter Inn, Newport Beach. Friday-Sunday.

August 29-30—**Hemodynamic Monitoring—Pulmonary Artery Catheterization.** Calif. Society of Anesthesiologists at Stanford Univ. Medical Center. Saturday-Sunday. 15 hrs. $275, CSA members; $325, nonmembers. Contact: Richard Manley, CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 29-September 5—**Concepts in Infertility—1981—Fifth Annual Edward Tyler Symposium.** Tyler Medical Clinic and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. Contact: Frank De Llyls, Astra Tours and Travel, 10929 Weyburn Ave., Los Angeles 90024. (213) 479-4444.

September 7-18—**Intensive Residency in Occupational Medicine, Session III.** UCSF. Two weeks.

September 19-20—**Eating Disorders.** UCLA. Saturday-Sunday.

September 21-23—**Spectrum of Recovery: From Conception Through the Golden Years.** Scripps Memorial Hospital, Alcoholism Treatment Center, at Islandia Hyatt, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+ hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

September 27-30—**Sports Medicine Now.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Wednesday. 22½ hrs. $200.

October 3—**2nd Annual Hyperbaric Symposium.** Sutter Community Hospitals at Holidome, Sacramento. Saturday. 7 hrs. Contact: Kristie Grieves, (916) 454-2222, ext. 1673.

October 7-10—**1981 Western Occupational Health Conference.** Western Occupational Medical Assn. at Doubletree Inn, Monterey. Wednesday-Saturday. Contact: Joseph Donovan, Exec. Dir., WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 12-13—**Alcoholism and the Family.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Monday-Tuesday. 12 hrs. $85.

October 12-16—**Clinical Update.** American Medical Assn. at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Dept. of Meeting Services, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 16—**2nd Annual Neurosciences Symposium: Current Concepts for Non-Neurologists.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 19-22—**British Medical Association Congress.** Town and Country Hotel, San Diego. Monday-Thursday. 10 hrs. through UCSD. Contact: Mr. G. Denney, Assoc. Exec. Dir., San Diego Co. Med. Soc., 3702 Ruffin Rd., San Diego 92123. (714) 565-8888.

October 22-24—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** See Psychiatry, October 24.

October 25-28—**California Academy of Family Physicians—Annual Meeting.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: William Rogers, CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

October 31—**Introduction to Traditional Chinese Medicine.** PMC. Saturday. 7 hrs. $125.

November 1-5—**American Public Health Association—109th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Thursday. Contact: APHA, 1015 15th St., NW, Washington DC 20005.

November 1-6—**American Congress of Rehabilitation Medicine**

and American Academy of Physical Medicine and Rehabilitation. Town and Country, San Diego. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., 30 N. Michigan Ave., Suite 922, Chicago 60602. (312) 236-9512.

November 2-6—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $325.

November 15—**Dilemmas With Drugs in Clinical Practice.** Granada Hills Community Hospital and UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 16-20—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

December 4-11—**Behavioral Medicine and Primary Care in the 80's.** Professional Institutes and Univ. of So. Carolina School of Medicine at Ilikai Hotel, Honolulu. One week. 16 hrs. $300. Contact: Jeri McClain, USC School of Medicine, Office for Academic Affairs, Columbia, SC 29208. (803) 777-7470.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

IDAHO

August 27-29—**Panhandle Emergency Medicine Conference II—5th Annual Scientific Session of the Idaho Chapter, American College of Emergency Physicians.** Coeur d'Alene. Thursday-Saturday. 12 hrs. Fee: $50-$115. Contact: Michael S. Carlson, MD, 3513 Pinehill Place, Coeur d'Alene, ID 83814. (208) 667-1771.

MONTANA

August 29—**Recent Advances in Diabetes Management.** East Glacier, Montana. Saturday. Glacier Park Lodge. 8:30 a.m. to 5:00 p.m. $40. Contact: American Diabetes Association, Montana Affiliate, Box 2411, Great Falls, MT 59403. (406) 761-0908.

October 1-3—**Annual Meeting of the Montana Medical Association.** Butte. Thursday-Saturday. Copper King Inn. Contact: Montana Medical Association, 2020 11th Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of tho Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 5-8—**Radiology for FP's—An Update.** Santa Fe. Wednesday-Saturday. Santa Fe Hilton Inn. 16 credit hours, also AAFP Prescribed. Contact: W. J. Levy, MD, Symposia de Santa Fe, PO Box 5175, Santa Fe, NM 87502. (505) 982-1911.

August 28—**The Menopausal Patient.** Albuquerque. Friday. Savage Auditorium, Presbyterian Hospital Center. 7 credit hours. Contact: Director of Medical Education, Presbyterian Hospital Center, 1100 Central SE, Albuquerque, NM 87106. (505) 843-9211.

September 3-5—**Sports Medicine.** Albuquerque. Thursday-Saturday. Location to be announced. 10 credit hours. Contact: Otto Appenzeller, MD, Dept. of Neurology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3342.

September 26—**Stroke and Spinal Cord Injuries.** Roswell. Saturday. Roswell Inn. 7 credit hours. Contact: W. J. Dean, MD, 813 North Washington, Roswell, NM 88201. (505) 622-2606.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

November 6—**Los Alamos Council for Cancer Annual Symposium for Colon Cancer.** Los Alamos. Friday. 16 credit hours. Contact: Philip H. Newman, MD, FACS, Los Alamos Surgical Associates Ltd., Los Alamos, NM 87544. (505) 662-3383.

November 13-14—**Interim Meeting, New Mexico Medical Society.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Scientific Program to be announced. Contact: New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 17-21—**The Grand Canyon Conference on the Treatment of Addictive Behaviors.** South Rim of Grand Canyon. Tuesday-Saturday. Grand Canyon National Park Lodges. Hour-for-hour credit. Contact: T. P. Bouble, Conference Coordinator, Division of Continuing Education & Commity Services, University of New Mexico, Albuquerque, NM 87131. (505) 277-2931.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue. Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (503) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8144.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland, OR 97201. (503) 225-7590.

OBSTETRICS AND GYNECOLOGY

October 1-3—**Fifth Annual Pacific NW Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

OPHTHALMOLOGY

October 1-2—**Vitrectomy.** Thursday-Saturday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

SURGERY

November 20—**Soft Tissue Surgery Techniques.** Friday. University of Oregon Health Sciences Center, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

September 11-12—**Gastroenterology: Current Concepts in Colon Disorders, Hepatitis and Obstructive Jaundice.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

September 25—**Second Annual Poisoning & Toxicological Emergencies Conference.** Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

November 12-13—**Symposium on Critical Care Medicine.** Thursday-Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland, OR 97201. (503) 225-8700.

December 4-5—**Urology for the Non-Urologist.** Friday-Saturday. Red Lion-Downtown, Portland. For additional information please contact: Division of Continuing Medical Education, University of Oregon Health Sciences Center, Portland OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

GRAND ROUNDS

SPONSOR: Primary Children's Medical Center
TITLE: **Pediatric Grand Rounds**
LOCATION: PCMC
DATE: First and third Thursdays—8:00 a.m.
CONTACT: Cathy Van Komen (801) 363-1221

SPONSOR: Utah Valley Hospital, Provo
TITLE: **Interdepartmental Grand Rounds**
LOCATION: UVH
CONTACT: Gary Watts, MD (801) 373-7850 (Ext. 2143)

* * *

August 14—**Health Effects of Air Pollution** (Sponsors: Intermountain Thoracic Society/American Lung Association/Utah Lung Association/UUMC). Salt Lake City. Friday. Hilton Hotel. 4 hrs. Fee: $15. Contact: Ms. K. Wiese (801) 581-5710.

September 3-5—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Thursday-Saturday. Tri-Arc Travelodge. 17 hrs. Fee: $300. Contact: Tricia Neilson, RN (801) 533-6435.

September 9-11—**Utah State Medical Association 86th Annual Scientific Session** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. 12 hrs. Fee: $50. Contact: Maxcine Fry (801) 355-7477.

September 12—**Exercise and Health** (Sponsors: 328th General Hospital, USAR at Ft. Douglas/Surgeon General's Office, US Army). Salt Lake City. Saturday. Hotel Utah. 6 hrs. Fee: $25. Contact: Kent Porter, Major, MCS (801) 582-4181.

October 9—**Topics in Pharmacology—Regional Joint ACP-ASIM Meeting** (Sponsor: University of Utah). Salt Lake City. Friday. Hilton Hotel. Hrs. to be announced. Fee: $20. Contact: Gregory A. Schwitzer, MD (801) 581-7818.

October 16-27—**Western Mediterranean Air/Sea Cruise and Medical Seminar** (Sponsors: Washington University School of Medicine (St. Louis)/Utah State Medical Association). Portugal, Morocco, Gibraltar, Spain, Italy, France. Friday-Tuesday. 27 hrs. Fee: $250 (Medical Seminar Registration Only). Contact: Maxcine Frey (801) 355-7477.

November 2-7—**Training and Certification of Pulmonary Function Testing** (Sponsor: UUMC). Location to be announced. Monday-Saturday. 17.5 hrs. Fee: To be announced. Contact: P. Lockey, MD (801) 581-3455.

November 6—**Renal/Pulmonary Syndrome — Postgraduate Course** (Sponsor: LDS Hospital). Salt Lake City. Friday. Hotel Utah. Hrs. and Fee to be announced. Contact: C. DuWayne Schmidt, MD (801) 350-1813.

November 13-14—**Advanced Tranma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Tri-Arc Travelodge. 17 hrs. Fee: $300. Contact: Tricia Neilson, RN (801) 581-7617.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 19 hrs. Fee: $200-$225. Contact: John L. Ninnemann, PhD (801) 581-7617.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

August 5-7—**Great Debates in Otolaryngology.** Seattle. Wednesday-Friday. Contact: U/W School of Medicine.

August 21-28—**Alaska Cruise: Strabismus.** Friday-Friday. Contact: U/W School of Medicine.

September 10-12—**Plastic Surgery for Primary Physicians.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: U/W School of Medicine.

September 15—**Gram Negative Infections and Antibiotics.** Scattle. Tuesday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 N. 120th, Scattle, WA 98133. (206) 364-0500, ext 1737.

September 16—**Spokane Internal Medicine Review.** Spokane. Wednesday evening. Sacred Heart Medical Center. Contact: U/W School of Medicine.

September 17-18—**Immediate Care of the Sick and Injured.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: U/W School of Medicine.

September 18—**Progress in Breast Cancer.** Seattle. Friday. Providence Medical Center. Contact: Evelyn Foote, Physician Education, Providence Medical Center, 500 17th Avenue C-34008, Seattle, WA 98124. (206) 326-5555.

September 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: UW School of Medicine.

September 21-25—**Advances in Family Practice.** Seattle. Monday-Friday. UW Kane Hall. Contact: U/W School of Medicine.

COURSE SPONSORS AND CONTACT INFORMATION

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 26-30, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1982—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: 1982—date and place to be announced.

September 25-26—**Annual Scientific Program.** Washington State Medical Association Annual Meeting. Friday-Saturday. Davenport Hotel, Sopkane, WA. Contact: Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801, or in-state toll-free at 1-800-552-0612.

September 26—**Orthopedics/Rheumatology.** Tacoma. Saturday. Contact: CME Pierce County.

October 1-3—**Advanced Cardiac Life Support.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

October 3—**Fifth Annual Cancer Symposium.** Tacoma. Saturday. Jackson Hall Medical Center Auditorium. Contact: Karen Tilley, Department of Oncology, Tacoma General Hospital, 315 South K Street, Tacoma, WA 98405. (206) 597-6965.

October 29-30—**Degenerative Joint Disease.** Seattle. Thursday-Friday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

November 7—**The Care of Aging Patients.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

November 7—**Medical Ethics.** Tacoma. Saturday. Contact: CME Pierce County.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

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★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON (See Advertising Page 19)**

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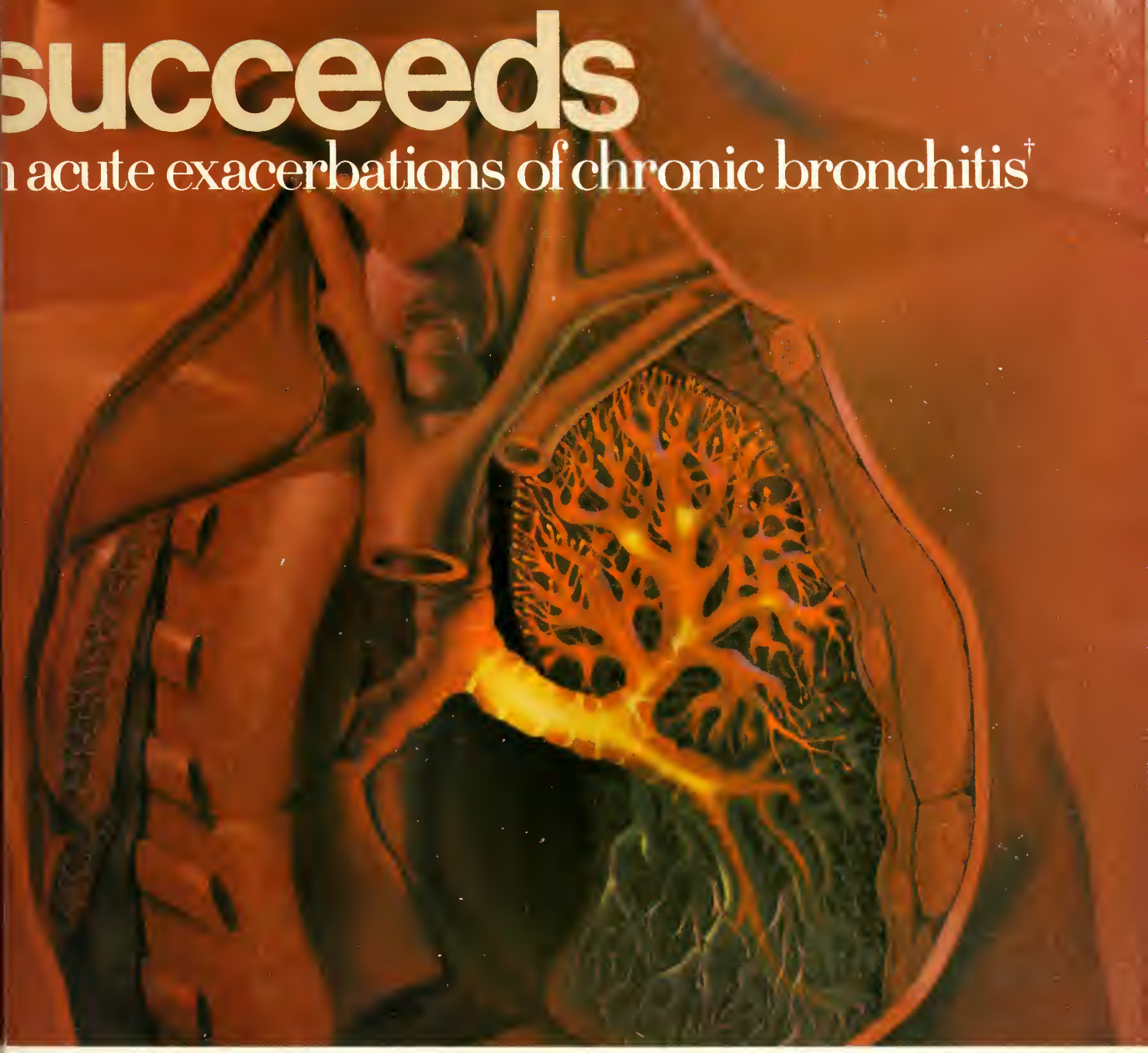

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Spin RH, Swartz MH *N Engl J*
303:426-432, Aug 21, 1980
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In controlled multicenter studies involving *H. influenzae* and *S. pneumoniae*, a 7-day follow-up after 14-day treatment showed the causative organisms were eliminated in 50 of 55 patients (91%).[2] Five patients did not return for follow-up.

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Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Note: The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides, patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term, nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus, infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended, therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General.* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients. *Pregnancy.* Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias.* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions.* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions.* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions.* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions.* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

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Children. Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

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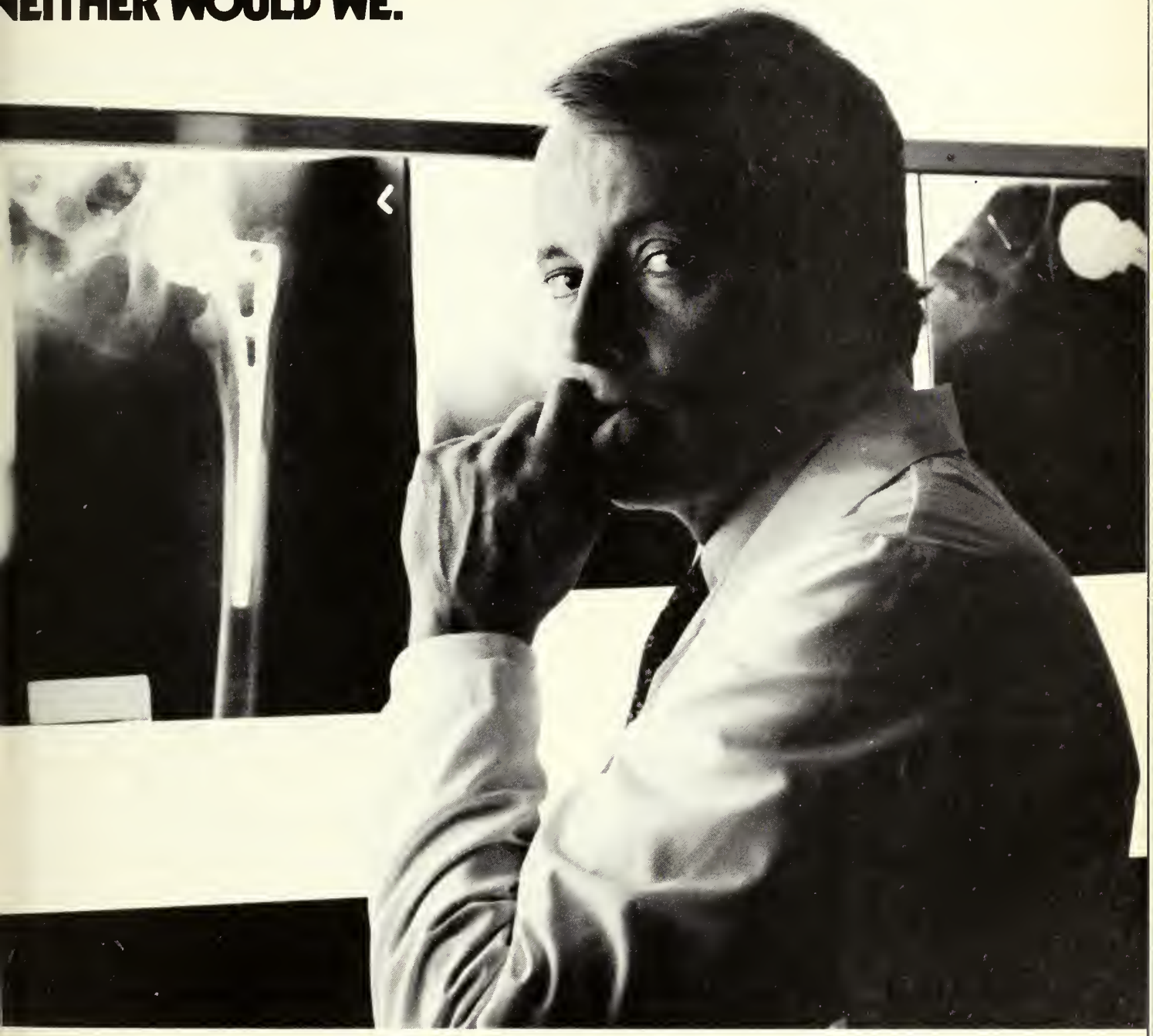

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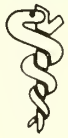

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SPECIALTY CONFERENCE

Spectrum of Human Chlamydial Infections
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From the Departments of Medicine and Pediatrics, Harbor-UCLA Medical Center, Torrance, California; Research and Medical Services, Veterans Administration Wadsworth Medical Center, Los Angeles; Department of Medicine, St. Mary's Medical Center, Long Beach, California, and the Departments of Medicine and Pediatrics, UCLA School of Medicine, University of California, Los Angeles, Health Sciences Center.

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Dr. Guze is a Research Associate, Veterans Administration Wadsworth Medical Center, and Associate Professor of Medicine, UCLA School of Medicine, Los Angeles.

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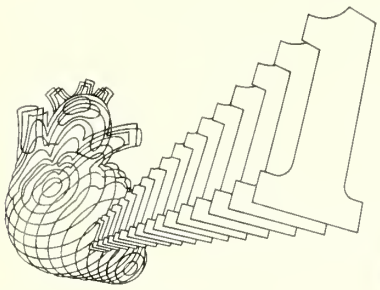

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Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence; decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss; emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual blood dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

SQUIBB

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★★ Official Journal of the California Medical Association
the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society
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and the Washington State Medical Association

Limiting the clinical complications of serious intra-abdominal infections

Acute appendicitis

In virtually all intra-abdominal infections, there is a recurring group of three anaerobes that are seen either singly or in combination, often mixed with aerobes.

This triad, composed of *Bacteroides fragilis*, clostridia, and anaerobic cocci (particularly peptostreptococci and peptococci) may complicate perforating appendicitis, abdominal trauma, and penetrating wounds.

Complications of *B. fragilis*

Complications such as thrombophlebitis, intra-abdominal abscess, and wound dehiscence may be explained by unique virulence factors elaborated by *B.fragilis*—the anaerobe most frequently encountered in anaerobic bacteremia and intra-abdominal sepsis.

Specific virulence factors

A capsular polysaccharide on the outer membrane of *B.fragilis* appears to differentiate it from other *Bacteroides* species. Experiments in animals have demonstrated that this polysaccharide alone can cause abscess. Other virulence factors produced by *Bacteroides* are heparinase and collagenase, which contribute to thrombophlebitis and wound dehiscence. Additional virulence factors that may enhance the pathogenicity of *B.fragilis* are lipases, proteases, nucleases, β-lactamases, and superoxide dismutase.

Clinical complications: penetrating abdominal wounds

In a prospective, randomized study at Cook County Hospital, Chicago, 100 patients who had penetrating abdominal wounds with spillage of bowel contents we given kanamycin (0.5 g q12h) and either clindamycin (600 mg q6h) o cephalothin (3 g q6h).[1] The clindamycin/kanamycin-treated group showed significantly fewer episodes of septicemia or intra-abdominal sepsis (see Table 1). The higher complication rate in th cephalothin/kanamycin group wa the result of infections due to

Intestinal anastomotic leak

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Acute colonic diverticulitis

anaerobic bacteria alone or a mixture of aerobes and anaerobes (see Table 2).

The cost of morbidity

fragilis was associated with complications in a majority of 335 patients with perforating appendicitis.[2] A retrospective review showed that these complications caused longer and more costly hospital stays and eater morbidity.

miting complications

intra-abdominal infections, these ta suggest that early, aggressive eatment with an antibiotic effec- e against anaerobes—especially ainst *B.fragilis* with its unusual ulence factors—may decrease orbidity and limit potentially life- reatening complications.

epalli H, et al. Abdominal trauma, anaerobes, and biotics. *Surg Gynecol Obstet* 137:270-276, 1973

er KS, Coll JA. The continuing challenge of perforating endicitis. *Surg Gynecol Obstet* 150:535-538, 1980

next page for brief summary rescribing information.

Table 1.—Septic Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Septic complications		
Septicemia	7	2
Intra-abdominal abscesses	7	3
Total complications	14	5

*Adapted from Thadepalli et al.[1]

Table 2.—Number of Anaerobe-Associated Infectious Complications in Patients with Traumatic Abdominal Injury*

	Cephalothin/Kanamycin (n = 52)†	Clindamycin/Kanamycin (n = 48)†
Mixed aerobes and anaerobes	6	0
Anaerobes	5	1
Totals	11	1

*Adapted from Thadepalli et al.[1]

†Dosage was 3 g cephalothin I.V. q6h and 0.5 g kanamycin I.M. q12h or 600 mg *Cleocin Phosphate* I.V. q6h and 0.5 g kanamycin I.M. q12h

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued (see WARNING box). A summary of prescribing information for *Cleocin Phosphate*—used in the treatment of serious infections due to anaerobic pathogens—can be found on the following page.

In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

Upjohn

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin base
benzyl alcohol	5 mg
disodium edetate	0.5 mg
water for injection	qs

When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis, and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. *Musculoskeletal:* Rare instances of polyarthritis have been reported.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin base. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

MED B-8-S

The Upjohn Manufacturing Company
Barceloneta, Puerto Rico 00617

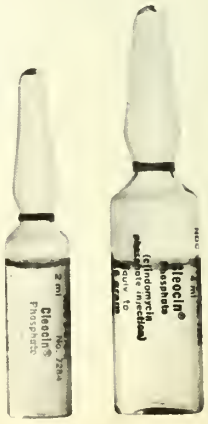
Upjohn

In serious intra-abdominal infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE



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If billing problems are hurting your income, turn to Bank of America's Professional Practice Management (PPM).

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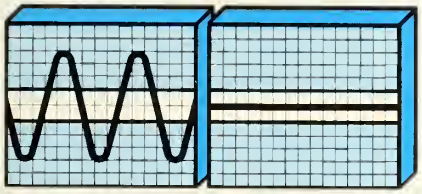
We straightened out the problem of theophylline blood levels.

THEO-DUR® (anhydrous theophylline)– The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours.

The problem with theophylline blood levels is that they are difficult to maintain in the therapeutic range and difficult to sustain for more than a few hours.

For most patients, the therapeutic range of theophylline is somewhere between 10 and 20 mcg/ml. If serum concentrations fall much below 10, theophylline is often ineffective. If they go much above 20, they are usually toxic.



Other oral theophyllines produce blood levels that float in and out of the therapeutic range

THEO-DUR produces linear blood levels that remain therapeutic

THEO-DUR is the only form of oral theophylline to offer linear serum concentrations. It minimizes the peak-trough fluctuations common to many other oral theophyllines. Once titrated, linear serum concentrations assure that THEO-DUR will remain therapeutic.

And, since THEO-DUR maintains therapeutic blood levels for 12 hours, patients can enjoy a full day of normal activities and a night of uninterrupted sleep.

Zero-order THEO-DUR–a unique form of oral theophylline.

THEO-DUR produces linear serum concentrations because THEO-DUR has zero-order absorption. The drug is absorbed into the blood at a constant quantity per hour.

Other oral forms of theophylline have first-order absorption, in which the largest amount is absorbed in the first hour and proportionately smaller amounts thereafter.

When absorption varies, as it does with first-order drugs, protection can also vary. That's why first-order theophyllines can be toxic within the first few hours and subtherapeutic later on.

THEO-DUR–the practical benefits.

Your patient benefits from the maximum control provided by THEO-DUR in several important ways: exercise tolerance is increased, emergency hospital visits are less likely and concomitant therapy is usually unnecessary.

Dosage titration is easy to achieve.* THEO-DUR is the only sustained-action tablet in 200 mg as well as 100 and 300 mg strengths, and all tablets are scored for greater dosage flexibility.

THEO-DUR also enhances patient compliance–with an every 12 hour dosage schedule that's easier to remember.

**After three days, on a steady dose, serum concentrations should be monitored and appropriate dosage adjustments made, if necessary*

Please see next page for a summary of prescribing information.

THEO-DUR®

anhydrous theophylline

Sustained Action Tablets

Today's most widely-prescribed bronchodilator.

KEY PHARMACEUTICALS, INC.

THEO-DUR®

anhydrous theophylline

Sustained Action Tablets

300 mg 200 mg 100 mg

The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours.

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives

Pharmacologic Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels Theophylline also possesses other actions typical of the xanthine derivatives coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation

Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity, serum theophylline levels should be monitored to assure maximum benefit with minimum risk Incidence of toxicity increases at serum levels greater than 20 mcg/ml High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in, patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions Ventricular arrhythmias or seizures may be the first signs of toxicity Many patients who have higher theophylline serum levels exhibit a tachycardia Theophylline products may worsen pre-existing arrhythmias

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established This is, unfortunately, true for most anti-asthmatic medications Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves Use theophylline cautiously in patients with history of peptic ulcer Theophylline may occasionally act as a local irritant to G I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are

Gastrointestinal Nausea, vomiting, epigastric pain, hematemesis, diarrhea

Central Nervous System Headaches, irritability, restlessness, insomnia reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions

Cardiovascular Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 139. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

September 19-20—**Workshop on Anesthesia and Cardiovascular Surgery.** American Society of Anesthesiologists at Hilton, San Francisco. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 3-4—**Weekend Seminar.** Calif. Society of Anesthesiologists at Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

January 10-15—**Anesthesiology Update.** UCSD. Sunday-Friday.

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

September 25—**Workshop on Flexible Fiberoptic Sigmoidoscopy.** USC. Friday. 6 hrs. Contact: Katie Eisenberg, MPH, USC Comprehensive Cancer Center, Regional Activities Program, 1721 Griffin Ave., Los Angeles 90031. (213) 224-7416.

October 3—**Melanoma—Light on the Black Cancer.** USC. Saturday. 5½ hrs. $60.

October 9-11—**Blood Diseases and Cancer in Children.** See Pediatrics, October 9-11.

October 12-16—**Medical Oncology Review.** American College of Physicians at Princess Kaiulani Hotel, Honolulu. Monday-Friday. 38¼ hrs. Contact: ACP, 4200 Pine St., Philadelphia 19104.

October 26-28—**Fifth Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 31—**4th Annual Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joann Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

October 31-November 1—**3rd Annual Symposium on Preventive Oncology: Cancer Prevention and Clinical Practice.** UCSF Continuing Education in Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

November 6—**Causes of Cancer.** Calif. Hospital Medical Center, Am. Cancer Soc., USC Cancer Management Network, at Biltmore Hotel, Los Angeles. Friday. $85. Contact: Kenneth Senter, MD, USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Phinney Hall 105, Los Angeles 90031. (213) 742-5750.

November 13-14—**Current Concepts on Cancer Management: Successful Treatment and Its Consequences.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $150, before Sept. 15; $200, thereafter. Contact: Office of Cont. Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

EMERGENCY MEDICINE

September 26—**Early Care of the Critically Injured Patient.** See Surgery, September 26.

September 28-29—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling can't stop moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard bone loss*.. the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. That it's not intended to treat nervous symptoms or depression associated with the menopause. That it can be very helpful in treating symptoms related to estrogen deficiency. You know how to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she really needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

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PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for Brief Summary of Prescribing Information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma—palliative therapy of advanced disease

9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens [19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens [17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement [19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction [23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users [31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives [33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nontatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives [36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression [2,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion.

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome; tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e g, three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically:* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically:* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100. No. 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K, *et al* N Engl J Med *293*:1167-1170, 1975 2 Smith, D C, *et al* N Engl J Med *293*:1164-1167, 1975 3 Mack, T M, *et al* N Engl J Med *294*:1262-1267, 1976 4 Weiss, N S, *et al* N Engl J Med *294*:1259-1262, 1976. 5 Herbst, A L, *et al*, N Engl J. Med *284*:878-881, 1971 6 Greenwald, P, *et al*: N Engl J Med *285*:390-392, 1971 7. Lanier, A, *et al* Mayo Clin Proc *48*:793-799, 1973 8 Herbst, A, *et al* Obstet Gynecol *40*:287-298, 1972 9 Herbst, A, *et al*: Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A, *et al*: N Engl J Med *292*:334-339, 1975 11 Stafl, A, *et al*: Obstet Gynecol. *43*:118-128, 1974 12 Sherman, A I, *et al* Obstet Gynecol *44*:531-545, 1974 13 Gal, I, *et al*: Nature *216*:83, 1967 14 Levy, E P, *et al* Lancet *1*:611, 1973. 15 Nora, J, *et al* Lancet *1*:941-942, 1973 16 Janerich, D T, *et al* N Engl J Med *291*:697-700, 1974 17 Boston Collaborative Drug Surveillance Program: N Engl J Med *290*:15-19, 1974 18 Hoover, R, *et al* N Engl J. Med *295*:401-405, 1976 19 Daniel, D G, *et al* Lancet *2*:287-289, 1967 20. The Veterans Administration Cooperative Urological Research Group. J Urol *98*:516-522, 1967 21 Bailar, J C Lancet *2*:560, 1967 22 Blackard, C, *et al* Cancer *26*:249-256, 1970 23 Royal College of General Practitioners J R Coll Gen Pract *13*:267-279, 1967 23a Royal College of General Practitioners Oral Contraceptives and Health, New York, Pitman Corp., 1974 24 Inman, W H.W, *et al* Br Med J *2*:193-199, 1968 25 Vessey, M P, *et al* Br Med J *2*:651-657, 1969 26 Sartwell, P E, *et al* Am. J Epidemiol. *90*:365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women N Engl J. Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women J A M A *231*:718-722, 1975 29 Mann, J I, *et al* Br Med J *2*:245-248, 1975 30 Mann, J I, *et al* Br Med J *2*:241-245, 1975 31 Inman, W H W, *et al* Br Med J *2*:203-209, 1970 32 Stolley, P D, *et al* Am J Epidemiol *102*:197-208, 1975 33 Vessey, M P, *et al* Br Med J. *3*:123-126, 1970 34 Greene, G R, *et al* Am J Public Health *62*:680-685, 1972 35 Coronary Drug Project Research Group J A M A *214*:1303-1313, 1970 36 Mays, E T, *et al* J A M A *235*:730-732, 1976 37 Pfeffer, R I, *et al* Am J Epidemiol *103*:445-456, 1976

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(Continued from Page 19)

October 2-3—**Symposium on Medical Emergencies.** UCLA at Miramar-Sheraton Hotel, Santa Monica. Friday-Saturday. 14 hrs. $180.

October 18-23—**Recognition and Management of Diving Casualties.** See Of Interest to All, October 18-23.

October 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

November 23-24—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 7-12—**Winter Sports Injuries.** See Of Interest to All, February 7-12.

February 12-13—**Toxicologic and Infectious Disease Emergencies.** UCLA. Friday-Saturday.

MEDICINE

September 18—**Diabetes and the Kidney—14th Annual Symposium on Renal Disease.** National Kidney Foundation of Northern Calif. at Hilton, San Francisco. Friday. $60. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd., Burlingame 94010. (415) 697-0110.

September 18-20—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

September 19—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

September 24-26—**Office Dermatology.** STAN. Thursday-Saturday. 19 hrs. $275.

September 25-26—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112, (800) 525-8646.

October 3—**4th Annual Heart Symposium.** Northridge Hospital at Century Plaza Hotel, Los Angeles. Saturday. Contact: Dept. of Med. Ed., Northridge Hospital, 18300 Roscoe Blvd., Northridge 91328. (213) 885-8500.

October 3-4—**The Skin from A to Z.** UCSF. Saturday-Sunday.

October 3-10—**Cardiology—1981.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $350.

October 6-7—**48th Annual Fall Symposium and 13th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $125, AHA member; $150, nonmember. Contact: Mary Frances Flynn, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 6-9—**Advances in Internal Medicine.** American College of Physicians at Letterman Army Institute, San Francisco. Tuesday-Friday. 22 hrs. Contact: ACP, 4200 Pine St., Philadelphia 19104.

October 7-9—**Current Neurology.** Straub Clinic and Hospital at Honolulu Art Academy, Honolulu. Wednesday-Friday. 12 hrs. $175. Contact: Office of Medical Administration, Straub Clinic and Hospital, 888 S. King St., Honolulu 96813.

October 9-10—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. $50/day. Contact: Paul H. Jacobs, MD, Derm. Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

October 9-11—**California Society of Internal Medicine—Annual Meeting.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Carol Parlette, Exec. Dir., CSIM, 703 Market St., Suite 1412, San Francisco 94103.

October 10—**Clinics in Medicine—Cardiology.** PMC. Saturday. 3 hrs. $40.

October 12-16—**An Advanced Course for Internists.** STAN. Monday-Friday. 25 hrs.

October 14—**Thrombophlebitis and Thromboembolic Disease.** LLU. Wednesday. 4 hrs.

October 14-December 16—**Nephrology.** UCLA. Wednesday evenings.

October 15-17—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday.

October 16—**2nd Annual Neurosciences Symposium: Current Concepts for Non-Neurologists.** See Of Interest to All, October 16.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 17—**Pediatric Allergy: Principles and Management.** See Pediatrics, October 17.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 19-22—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Mark Hopkins Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

October 21—**Endocrine—Third Annual Symposium.** The Hospital of the Good Samaritan at Hyatt Regency, Los Angeles. Wednesday. 7 hrs. $75. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 24—**Allergy/Immunology.** PMC. Saturday. 6 hrs.

October 24-25—**Diabetes Workshop.** UCSF. Saturday-Sunday.

October 24-31—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

October 28-30—**Neurology for the Internist and Family Physician.** USC at Marriott Hotel, Newport Beach. Wednesday-Friday. 24 hrs. $250.

(Continued on Page 38)

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(Continued on Page 28)

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(Continued on Page 34)

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The Clinical Spectrum of Toxic Shock Syndrome

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Toxic shock syndrome (TSS) is a recently recognized acute multisystem illness that may recur. Epidemiologic links with menstruation and use of tampons have been identified. We report the cases of seven patients (six women and one man), 12 to 31 years old, seen over nine months, who met the criteria for TSS. Four were menstruating at onset. All had hypotension, fever, erythematous rash and distal desquamation. A prodrome of myalgias and diarrhea occurred in all patients. Clinical features of the acute illness included pharyngitis, conjunctivitis, leukocytosis and renal dysfunction (7), hepatobiliary abnormalities (6), mental confusion (6) and coagulopathy (4). In three patients, examination of cerebrospinal fluid showed abnormalities. The illness progressed in three patients to adult respiratory distress syndrome and significant cardiac dysfunction. Staphylococcus aureus *was isolated from mucosal sites in six. The disease recurred in two. There were no deaths. Possible transmissibility was illustrated by two patients, a married couple, with simultaneous illnesses. Pathophysiologic features of TSS suggest a toxicogenic cause. Management consists of early recognition, vigorous fluid resuscitation, inotropic support as needed, discontinuation of tampon use and treatment with antistaphylococcal antimicrobic drugs.*

TOXIC SHOCK SYNDROME (TSS) is an acute febrile illness involving multiple organ systems and associated with hypotension and rash. Since this entity was first described in 1978,[1] a striking increase in reported frequency has occurred.[2-7] Epidemiologic data indicate an association with menstruation and, in particular, the use of tampons.[3,4] *Staphylococcus aureus* has been isolated from mucous membranes of affected patients, but the cause of TSS remains unclear. However, the clinical features of the syndrome suggest a toxicogenic cause.

Between December 1979 and August 1980 we saw seven patients, admitted to the University of California, Davis (UCD), Medical Center in Sacramento, whose illnesses were consistent with a diagnosis of TSS. The diagnoses were made in conformity to a definition of the syndrome recently proposed by the Surgeon General of the United

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
BUN = blood urea nitrogen
CPK = creatine phosphokinase
CSF = cerebrospinal fluid
DIC = disseminated intravascular coagulation
GGT = gamma glutamyl transferase
LDH = lactate dehydrogenase
MLNS = mucocutaneous lymph node syndrome
PCWP = pulmonary capillary wedge pressure
PEEP = positive end-expiratory pressure
PT = prothrombin time
PTT = partial thromboplastin time
SEB = staphylococcal enterotoxin B
TSS = toxic shock syndrome
UCD = University of California, Davis

States. The criterial which must be fulfilled to meet this definition are outlined in Table 1.

Our experience with these seven patients illustrates not only the potential seriousness of the illness but also the wide clinical spectrum of the syndrome. Several patients with acute, life-threatening diseases are included in this series. Recurrent disease with variably severe symptoms occurred in two of the patients. Finally, two patients, one of whom was male, show a potential for either transmissibility or common-source acquisition of the syndrome that, to our knowledge, has not previously been reported.

The following selected cases are representative of the broad range of clinical involvement seen in TSS.

Reports of Cases

CASE 1. A 19-year-old woman, previously in good health, was admitted to the UCD Medical Center in shock. Six days earlier, she had sustained second degree facial burns, which had been treated topically with silver sulfadiazine. Three days before admission, nausea, vomiting and watery diarrhea developed. On the morning of admission, she woke with painful, cold extremities and profound weakness. There was no history of fever, chills, exposure to infectious diseases, travel or intravenous use of drugs. Menses had been regular, with the last period 20 days previously.

On admission, she appeared acutely ill, with a pulse of 140 beats per minute, no palpable blood pressure, respiratory rate of 40 per minute and a temperature of 39.1°C (102.4°F). She was confused and complained of severe myalgias in her back and legs. Second degree burns without exudate were present on the face, and an evanescent erythematous macular rash was seen on the trunk and thighs. There was bilateral purulent conjunctivitis. The nose, mouth and throat were dry and the tongue was coated and pink. The neck was supple. There was no lymphadenopathy. Both lung fields were clear. The heart sounds were normal without murmurs or extra sounds. Initial examination of the abdomen disclosed diffuse tenderness with normal bowel sounds; however, two hours later, bowel sounds were absent. Pelvic examination showed no abnormalities except for a thin white vaginal discharge. The extremities were cold with poor capillary filling.

Initial laboratory values were as follows: leukocyte count 20,900 per cu mm (50 percent segmented neutrophils, 43 percent band neutrophils, 2 percent lymphocytes, 4 percent metamyelocytes and 1 percent myelocytes); blood urea nitrogen (BUN) 37 and creatinine 2.4 mg per dl; sodium 134, potassium 4.2, chloride 94 and carbon dioxide 14 mEq per liter; serum aspartate aminotransferase 140 IU per liter; bilirubin 1.8 mg per dl; serum amylase 148, lactate dehydrogenase (LDH) 425, gamma glutamyl transferase (GGT) 60 and creatine phosphokinase (CPK) 4,180 IU per liter (MB fraction less than 1.5 percent); lactate 1.2 mEq per liter; prothrombin time (PT) 13.7 sec (control 11.5); partial thromboplastin time (PTT) 51.4 sec (control 35 to 40) and fibrinogen 380 ± 25 mg per dl. Fibrin monomers and fibrin split products were not detected. Analysis of urine showed 1+ proteinuria; 25 to 50 erythrocytes and 12 to 25 leukocytes per high-power field, and 2+ bacteriuria. The cerebrospinal fluid (CSF) contained 10 leukocytes per cu mm (8 polymorphonuclear neutrophils and 2 mononuclear cells), glucose 59 mg per dl and protein 19 mg per dl. No organisms were seen on Gram stain. An electrocardiogram showed sinus tachycardia. An x-ray study of the chest showed no abnormalities.

Treatment was initiated with intravenously

TABLE 1.—*Criteria for the Diagnosis of Toxic Shock Syndrome**

- Fever (temperature ≥38.9°C [102°F])
- Erythematous macular rash
- Desquamation during recovery phase
- Systolic blood pressure of 90 mm of mercury or lower for an adult
- Involvement of at least four organ systems
- Reasonable evidence for the absence of meningococcal infection, Rocky Mountain spotted fever, bacteremia or other known diagnostic possibility

*Adapted from Update on Toxic-Shock Syndrome. FDA Drug Bulletin 10:3 Nov 1980.

given normal saline and methylprednisolone 30 mg per kg of body weight, followed by three doses (15 mg per kg of body weight) at six-hour intervals; nafcillin 150 mg per kg of body weight, gentamicin 5 mg per kg of body weight and chloramphenicol 65 mg per kg of body weight were given per day. Initial hemodynamic measurements after insertion of a Swan-Ganz catheter included the following: central venous pressure 9 and pulmonary capillary wedge pressure (PCWP) 12 mm of mercury; cardiac output 8.7 liters per minute; systemic vascular resistance 388 and pulmonary vascular resistance 46 dyne•sec•cm^{-5}, and mixed venous oxygen tension 45 mm of mercury. Heart rate was 120 per minute and blood pressure 68/40 mm of mercury following administration of 11 liters of fluid during the first three hours. Dobutamine and large volumes of crystalloid were required to maintain the systolic blood pressure at 85 mm of mercury during the first 36 hours.

Hypoxic respiratory failure occurred on the second hospital day, requiring intubation and mechanical ventilation with positive end-expiratory pressure (PEEP). Additionally, the cardiac output fell to 3.6 liters per minute and remained low until day 4. Tests for disseminated intravascular coagulation (DIC) remained abnormal for seven days. The feces became guaiac-positive and the hematocrit fell to 15.8 percent, necessitating blood transfusion. Jaundice was noted on day 4. A gall bladder scan showed normal biliary function.

Initial blood, urine and CSF cultures yielded no growth. Cultures of the feces grew 3+ coliforms. *Staphylococcus aureus* in pure culture was isolated from swabs of the facial burn and the conjunctival exudate. Cultures of cervix and vaginal discharge were negative for *S aureus* and *Neisseria gonorrhoeae,* as were cultures of throat and rectal swabs.

She improved gradually during the second week and was extubated on day 13. After a convalescence complicated by pulmonary embolism she was discharged on day 26. Two weeks after discharge, desquamation of the palms and soles occurred, and an area of alopecia on the scalp was noted. There has been no recurrence of illness in eight months of follow-up, but progessive diffuse alopecia of the scalp persisted for six months.

CASE 2. A 30-year-old woman was admitted to hospital in shock. Two days earlier the sudden onset of watery diarrhea and vomiting had occurred. Abdominal pain, myalgias and arthralgias developed. On the day of admission, a rash appeared on the extremities. Treatment, consisting of fluid resuscitation and intravenous administration of penicillin and amikacin, was initiated after blood, urine and CSF specimens for culture had been obtained in another hospital, and the patient was transferred to the UCD Medical Center.

A physical examination on admission showed an acutely ill woman with a blood pressure of 70/50 mm of mercury, pulse 112 per minute and temperature 36.3°C (97.6°F). A macular petechial rash was present on the forearms and lower extremities. The neck was supple. The conjunctivae were injected, and the pharynx was dry and injected without exudate. No lymph nodes were palpable. Both lung fields were clear. Findings of a cardiovascular examination were within normal limits except for hypotension, tachycardia and somewhat diminished pulses in the cool, moderately cyanotic extremities. The abdomen was diffusely tender with decreased bowel sounds; no masses or enlarged organs were palpated. Pelvic examination was normal except for thick vaginal discharge containing a small amount of blood. A neurologic examination showed no abnormalities.

Laboratory data were as follows: leukocyte count 14,600 per cu mm (31 percent segmented neutrophils, 48 percent band neutrophils, 5 percent lymphocytes and 1 percent metamyelocytes); serum creatinine 3.9 and BUN 58 mg per dl; serum asparate aminotransferase 120, LHD 364 and GGT 584 IU per liter, and albumin 2.3 grams per dl. The PT was 13.3 sec (control 11.0 sec), PTT 57.4 sec (control 35 sec), fibrinogen 220 mg per dl and fibrin split products positive in a titer of 1:40. The platelet count was 48,000 per cu mm. Analysis of urine showed blood and albumin, with 6 to 12 leukocytes per high-power field seen in the sediment. A study of CSF showed no abnormalities.

A Swan-Ganz catheter was inserted, and the PCWP was 12 mm of mercury following volume resuscitation. Cardiac output by thermodilution was 7.5 liters per minute.

Penicillin, tobramycin and chloramphenicol, as well as methylprednisolone, were given. Vigorous intravenous fluid therapy and inotropic agents were required during the first 48 hours. Fever developed (temperature to 39.3°C [102.7°F]) on day 2 and persisted for ten days. Pulmonary infiltrates, hypoxemia and progressive decrease in lung compliance appeared on day 3, requiring intubation and institution of mechanical ventilation

with PEEP. On day 4, the platelet count fell to 12,000 per cu mm, and platelets were transfused. Bilateral pleural effusions containing 25,200 erythrocytes and 1,400 leukocytes per cu mm (2 percent polymorphonuclear neutrophils) and having the biochemical characteristics of a transudate developed.

Cultures of blood, CSF, urine, pleural fluid, feces, skin lesions and vaginal secretions were negative. In addition, the CSF was negative for serological evidence of pneumococcal, meningococcal or *Hemophilus influenzae* antigen by counterimmunoelectrophoresis. *S aureus* was isolated from nasopharyngeal cultures. Bone marrow, examined at the nadir of thrombocytopenia was hypercellular, with granulocytic hyperplasia and normal megakaryocyte content. Titers of antibody to *Herpes simplex* virus, type 1 (HSV-1) showed a fourfold increase, but other viral titers were negative.

The patient's hospital course in the second week of illness was one of gradual improvement. Antimicrobic drugs were discontinued on days 5 (chloramphenicol) and 14 (penicillin and tobramycin). Skin lesions cleared without scarring. She was discharged on day 19 and when seen a month later reported patchy alopecia, desquamation of the palms, soles, face and neck, amenorrhea and easy fatigability.

CASE 3. A 31-year-old man was the husband of the patient described in case 2. An identical illness developed the same day as his wife's, though diarrhea was more severe in his case.

Initially, the clinical features were similar to those of his wife, with pronounced hypotension, tachycardia and diffuse muscle tenderness. Several purpuric lesions were noted over his patellae and the dorsa of the feet, but, in general, he did not have the striking petechial rash that developed in his wife. A mucopurulent conjunctivitis was present. On day 2, a brightly erythematous and diffuse macular rash appeared on his trunk.

Laboratory findings in this patient were similar to those seen in case 2, except that pronounced thrombocytopenia did not develop. Results of CSF examination were slightly abnormal, with 5 leukocytes per cu mm (3 polymorphonuclear neutrophils and 2 mononuclear cells) but normal protein and glucose values. On day 2, there were 22 leukocytes per cu mm (19 mononuclear cells) noted, with other CSF values normal. Cultures of blood, CSF, urine and feces were negative. Conjunctival cultures were positive for *Staphylococcus epidermidis*. Viral titers showed a fourfold rise against HSV-1.

The clinical course of the disease in this patient was otherwise similar to that described in case 2; mental confusion developed and cleared after a week, and respiratory complications were less severe. Treatment was the same in both cases.

Discussion

The clinical diagnosis of TSS is based on the criteria listed in Table 1. The cases of our seven patients (six women and one man, aged 12 to 31 years) met these criteria and demonstrate the clinical spectrum of this syndrome. A prodrome of malaise, myalgias and watery diarrhea progressed to an acute systemic illness with fever, hypotension, pharyngitis, conjunctivitis, leukocytosis and rash with subsequent desquamation in all patients. Four of the seven were menstruating at the time of admission to the hospital.

Three patients were moribund when admitted to our hospital and required massive crystalloid infusions to achieve and maintain blood pressures of 80 to 85 mm of mercury systolic. Further, in these three, adult respiratory distress syndrome (ARDS) developed, which required intubation, mechanical ventilation with high fraction of inspired oxygen (FIO_2) and PEEP. In contrast, the other four patients were acutely ill but responded very well to less invasive supportive measures. Two of them (patients 4 and 6) clearly had manifestations of the disease a month before admission and had been managed adequately as outpatients. There were no deaths or significant sequelae in our series.

The range of systemic involvement in this multisystem illness is broad (see Table 2). All patients had cardiovascular collapse at the time of admission. Four responded to mild fluid resuscitation while two had evidence of profound myocardial dysfunction and three required inotropic support with dobutamine. Swan-Ganz catherization in three patients showed low to normal PCWP and, initially, high cardiac outputs that quickly fell in two of these three. The CPK was elevated in four patients; however, when the myocardial fraction was assayed in patient 1, it was consistently below 1.5 percent of the total CPK.

Renal dysfunction was present in all patients. Sterile pyuria, hematuria and azotemia were seen in six patients and proteinuria in four. All renal abnormalities resolved after fluid resuscitation, suggesting that prerenal factors may have been

predominant in the pathogenesis of these findings. No urinary infection was found.

Hepatobiliary abnormalities occurred in six patients, characterized by elevated levels of transaminases, GGT and alkaline phosphatase. Hyperbilirubinemia occurred in five patients. A radionuclide gall bladder scan in patient 1 demonstrated a functioning biliary tract and a follow-up chole-

TABLE 2.—*Clinical and Laboratory Manifestations of Toxic Shock Syndrome in Seven Patients*

Prodrome	*Patients* 1	2	3	4	5	6	7
Gastrointestinal							
Nausea and vomiting	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	+
Mucosal							
Conjunctivitis	+	+	+	+	+	+	+
Pharyngitis	+	+	+	+	+	+	+
Glossitis	+	−	+	+	+	+	+
Vaginitis discharge	−	+	0	+*	+	+	+
Menstruating at onset	−	−	0	+	+	+	+
Fever (temperature ≥38.9°C [102°F])	+	+†	+	+	+	+	+
Cardiovascular							
Hypotension (BP <90 mm of mercury systolic)	+	+	+	+	+	+	+
Tachycardia (P>110 beats/min)	+	+	+	+	+	+	+
Peripheral cynanosis	+	+	+	−	+	−	−
Myocardial depression (CI <3.3 L/min/m²)	+	+	−	NA	NA	NA	NA
Respiratory							
Adult respiratory distress syndrome	+	+	+	−	−	−	−
Hypoxemia (Po_2 <50 Torr)	+	+	+	−	NA	NA	NA
Required mechanical ventilation	+	+	+	−	−	−	−
Renal							
Azotemia (creatinine 1.6 mg/dl)	+	+	+	+	+	−	−
Proteinuria	+	+	NA	+	−	+	−
Hematuria	+	+	NA	+	+	+	−
Pyuria	+	+	NA	+	+	+	+
Hepatobiliary							
Hepatomegaly	+	−	−	−	+	+	+
SGOT >2×normal	+	+	+	NA	+	+	+
Bilirubin >1.6 mg/dl	+	−	−	NA	+	+	+
Amylase >150 IU/liter	+	−	−	+	−	+	−
Hematologic							
Leukocytosis (leukocytes >14,000/cu mm)	+	+	+	+	+†	+	+
Thrombocytopenia (platelets <10⁵/cu mm)	+	+	+	NA	−	−	−
PT and PTT >4 standard deviations above normal	+	+	+	NA	+	NA	−
Musculoskeletal							
Myalagias	+	+	+	+	+	+	+
Arthralgias	+	+	+	+	−	+	+
CPK >2×normal	+	−	+	NA	+	+	NA
Neurologic							
Delirium	+	+	+	+	+	−	+
Aseptic meningitis	+	−	+	−	+	NA	NA
Recovery phase							
Rash	+	+	+	+	+	+	+
Desquamation	+	+	+	+	+	+	+
Patchy alopecia	+	+	+	−	−	−	+
Recurrent attacks	−	−	−	+	−	+	−
Amenorrhea	+	+	0	−	NA	−	−
Staphylococcus aureus isolated							
Vagina	−	−	0	+	+	+	+
Other mucosal site	+‡	+§	−	−	−	−	−

BP = blood pressure; CI = cardiac index; CPK = creatine phosphokinase; NA = data not available; P = pulse; Po_2 = partial pressure of oxygen; PT = prothrombin time; PTT = partial thromboplastin time; SGOT = serum glutamic oxaloacetic transaminase (serum aspartate aminotransferase); + = positive findings; — = negative findings; 0 = not applicable.

*First episode only.
†Developed on second hospital day.
‡Conjunctiva, facial burns.
§Nasopharynx.

cystogram (after oral administration of contrast medium) in patient 6 showed a normal gall bladder. Clinical pancreatitis with hyperamylasemia developed in three patients. Diffuse abdominal tenderness was seen in six patients, although definite signs of peritonitis did not develop in any of them.

Disseminated intravascular coagulation with prolonged coagulation times and peripheral platelet consumption occurred in three patients, while a coagulopathy without platelet consumption was seen in a fourth. Gastrointestinal bleeding occurred in the three patients with DIC, requiring blood transfusion in patients 1 and 2. Additionally, patient 2 required platelet transfusions. A bone marrow aspirate done at the nadir of thrombocytopenia in patient 2 showed a hypercellular marrow with granulocytic hyperplasia but normal megakaryocytes. This suggests either relative suppression of megakaryocyte precursors, with or without peripheral platelet consumption, or failure of platelet release from the bone marrow.

Six patients displayed delirium or mental confusion, severe enough in two to necessitate the use of soft restraints for self-protection. Three patients with abnormal CSF also had clinical courses consistent with aseptic meningitis. Counterimmunoelectrophoresis of the CSF failed to detect antigens of *N meningiditis, S pneumoniae* or *H influenzae*. CSF cultures for bacteria and fungi were negative in all cases. All patients recovered without neurologic sequelae.

Diffuse and severe myalgias were a prominent complaint in six patients, with pronounced muscle tenderness persisting as long as seven to ten days a frequent finding. Although several of our patients also experienced intermittent arthralgias, none manifested inflammatory arthropathies.

In six of our patients, *S aureus* was isolated from mucous membranes. Four of these isolates were from vaginal secretions, all in menstruating women. Of the two women with negative vaginal cultures, one was not menstruating at the onset of illness (patient 1) and one did not have vaginal cultures taken until the third day of illness and after antimicrobial drugs had been given (patient 2). One woman (patient 1) had *S aureus* isolated from the conjunctivae as well as from clean facial burns; in patient 2, the organism grew from nasopharyngeal swabs. In no patient was staphylococcal bacteremia observed.

The convalescent phase of TSS was characterized by recurrence of disease with menses in two patients in whom *S aureus* had been isolated in vaginal cultures and by amenorrhea in two others. Additionally, prominent patchy alopecia was observed in four patients, which lasted six months in patient 1. All patients experienced distal desquamation within two weeks of the onset of illness. The findings we report are in agreement with those of others who have described the clinical features of TSS.[3-5,8,9]

Cause and Pathogenesis

The precise cause and pathogenesis of TSS are as yet unknown. However, the similarity between TSS and so-called staphylococcal scarlet fever,[10-12] the lack of demonstrable bacteremia in patients otherwise having all the hallmarks of septic shock, and the association with *S aureus* colonization or local infection strongly suggest a contributory or causal role for staphylococcal exotoxin or exotoxins. *Staphylococcus aureus* isolates from five patients in Todd's series produced an epidermal toxin, which those authors suggested might account for the characteristic skin involvement in TSS.[1] A different pyrogenic exotoxin derived from *S aureus* has been described and characterized by Schlievert and co-workers.[13] The original isolate that produced this toxin was grown from vaginal cultures of an adult patient diagnosed as having Kawasaki's disease.[14] In retrospect, the clinical manifestations in that patient were entirely compatible with TSS. Distinct from other known staphylococcal toxins, the toxin isolated from this patient's organism produced fevers in both rabbits and mice, was a potent mitogen but did not produce exfoliative changes in suckling mice. Further, Schlievert observed enhanced host susceptibility to damage by endotoxin—"either lethal shock or myocardial and liver damage."[13]

The possibility of a toxin or toxins either directly or indirectly causing the multisystem failure seen in TSS is an attractive hypothesis. In three of our patients the course was consistent with severe toxicogenic shock. Each of these patients was in shock when admitted to hospital and massive fluid resuscitation was required to achieve normal cardiac filling pressures. Initially, cardiac output was elevated but fell rapidly, with pronounced cardiac dysfunction and persistently low systemic vascular resistance. Elsberry and his colleagues[15] have described similar findings in monkeys with either staphylococcal enterotoxin B

(SEB) or endotoxin from *Escherichia coli*. Shock caused by *E coli* endotoxin occurred rapidly and resulted in increased systemic vascular resistance. Conversely, in the shock associated with SEB, the cardiovascular collapse occurred more slowly and systemic vascular resistance consistently remained slightly below normal.[15] This model is consistent with findings observed in our patients. The slower onset of cardiovascular collapse with SEB may explain why TSS patients have a prodrome of several hours before presenting in shock. Additionally, the persistently low systemic vascular resistance observed with SEB is consistent with similar findings in our patients.

The gastrointestinal symptoms early in the course of TSS are similar to those reported in staphylococcal toxin-mediated gastroenteritis. Subsequent hepatocellular dysfunction, hyperamylasemia and gastrointestinal bleeding are most likely related to the hypotension during the shock phase of TSS and the resultant development of DIC. Whether the hematologic abnormalities are directly related to the presence of a toxin, or are a result of microvascular phenomena induced by shock is unclear. It seems probable that the dermatologic findings in TSS also have a toxicogenic basis, but support for this contention must await more definitive characterization of the responsible agent or agents.

Epidemiologic studies have pointed out a statistical association between tampon use and the development of TSS.[3] Asymptomatic vaginal ulcerations have been described in tampon users.[16] *Staphylococcus aureus* has been found in the normal vaginal flora of 5 percent of women.[17] Ulceration of the vaginal mucosa as a result of tampon use may provide the point of entry for *S aureus* or its exotoxin. However, in 42 percent of our patients we were unable to implicate vaginal *S aureus*. Thus, the vaginal mucosa, although perhaps a common site, is not the exclusive point of entry of toxin. Isolation of *S aureus* from de-epithelialized skin in our first patient raises the possibility that colonization of compromised tissue at any site may result in an environment favorable to generation and absorption of a toxin or toxins. Such a mechanism may have been responsible for the development of TSS in Todd's and earlier cases,[1,10,11] in which TSS occurred in association with focal staphylococcal infections.

Transmissibility is suggested by our cases 2 and 3: TSS developed in the husband within 12 hours of the disease's occurrence in his wife. *Staphylococcus aureus* was cultured from a mucosal site in the wife but could not be cultured from the husband. No other causative or epidemiologic factors could be implicated to account for their illnesses, which were virtually identical in presentation and course and fulfilled all the criteria for TSS. To our knowledge, this is the first reported case of TSS in a consort.

Some investigators have raised the possibility of viral synergy in the pathogenesis of TSS,[8] and several reports have described either clinical or serological evidence of infection with herpesvirus concomitant with the acute illness.[6,8] In cases 2 and 3 there was a fourfold rise in viral titers against HSV-1, without clinical evidence of local or disseminated infection. It is unclear whether this represents a nonspecific response to acute illness, a concurrent subclinical infection or a potential predisposing factor to the development of TSS.

In only one of our patients (case 5) was lymphadenopathy present. Interestingly, in this our youngest patient, the manifestations combined features of TSS and the mucocutaneous lymph node syndrome (MLNS) or Kawasaki's disease.[18] MLNS is characterized by fever unresponsive to antimicrobic drugs, conjunctivitis, pharyngitis, strawberry tongue, fissured lips, peripheral edema, cervical lymphadenopathy and desquamative erythematous rash on the extremities. The major differences between TSS and MLNS are the hypotension associated with TSS, and the lymphadenopathy and indurative nature of the rash on the extremities in MLNS. Recently, several cases of MLNS have been reported in adults.[14,19-23] Most, if not all, of these cases also fit the criteria for TSS. Significant hypotension was a presenting feature in most of the patients with "adult Kawasaki disease." Cardiac dysfunction has been reported in 5 percent to 15 percent of patients with MLNS.[24,25] It is tempting to speculate that a similar mechanism of staphylococcal toxin-mediated myocardial damage links these cases with those in our series who had evidence of significant myocardial dysfunction. Patchy alopecia in the recovery period, as observed in several of our patients, has also been reported in MLNS.[25] Twenty-five percent of the patients reported by Kawasaki in 1974 had *S aureus* isolated from throat cultures,[18] another finding that guides speculation on the possible relationship of these syndromes in a spectrum of

Staphylococcus-associated diseases. Further study will be required to establish the likelihood of such a relationship.

Prevention

Strategies for the prevention of TSS remain of unproved value. Identification of those at high risk of contracting TSS by virtue of vaginal carriage of *S aureus* is a possible approach that cannot be justified until more data on the carriage rate in the normal population have been accumulated. Moreover, such an approach would not aid in identifying potential victims whose disease is not associated with menstruation or a vaginal route of acquisition of the disease. However, in those at risk for recurrent disease, detection and eradication of vaginal *S aureus* should be considered. In view of the epidemiologic association with use of tampons and the recurrent nature of the illness, we have advised our TSS patients not to use tampons.

Treatment

Treatment of TSS must include recognition and early aggressive management of the life-threatening manifestations of the disease, specifically those related to the serious hemodynamic compromise that develops in most patients. Signs of myocardial dysfunction should be sought and monitored appropriately, and our experience points out the potential requirement for inotropic drug support in some patients. In view of the reports of serious cardiac sequelae in patients with MLNS and the possible relationship of that disease to TSS, patients with TSS who have cardiac dysfunction during their acute illness should be followed for several months, with careful attention paid to cardiac status. Although antimicrobial drug therapy has not been known to alter the course of the acute illness, a favorable effect on the incidence of recurrent disease, as suggested by some investigators, cannot be excluded.[3] Therefore, our practice is to include in the management of TSS treatment with a β-lactamase-resistant antistaphylococcal drug for seven to ten days.

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Ultrasonic Arteriography: Implications in Patient Management

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Forty-six consecutive studies of carotid bifurcations were done with a Hokanson Ultrasonic Arteriograph before contrast arteriography. Based on the Doppler signal and the oscilloscopic image, each internal carotid artery was sorted into one of four categories as an estimation of the percent diameter reduction: less than or equal to 10 percent, 10 percent to 49 percent, 50 percent to 99 percent, and total occlusion. These results were compared with the percent diameter reduction determined from contrast arteriograms by a vascular radiologist unaware of the noninvasive test results. Overall, 83 percent of the arteries were correctly categorized. Detection of stenosis in the 50 percent to 99 percent range was 89 percent accurate. The sensitivity and specificity in detecting a 50 percent or greater stenosis were both 96 percent.

STROKE REMAINS the third largest cause of death in the United States.[1] As many as 40 percent of these deaths are the result of arterial occlusive disease occurring at the carotid bifurcation.[2] In an effort to detect occlusive disease at this location, various noninvasive tests have been devised. Many have serious shortcomings, not the least of which are a lack of patient acceptance and accuracy rates that vary widely from investigator to investigator. One method, ultrasonic arteriography, has been shown by several investigators to have excellent accuracy and reproducibility as well as patient acceptance.[3-5] We present our results using the ultrasonic arteriograph as developed by Hokanson and discuss the implications such testing may have on patient management.

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Patients and Methods

From March 1979 through March 1980, 222 carotid arteries were evaluated with the Hokanson Ultrasonic Arteriograph Model P1 at the Seattle Veterans Administration Medical Center. This instrument uses a 5 MHz pulsed Doppler signal to detect blood flow. When flow is detected, a spot is illuminated on a storage oscilloscope that corresponds to the transducer coordinates. Sequential movement of the transducer in transverse and longitudinal planes results in illumination

of additional spots, creating a flow map of the underlying artery. The flow map and the audible interpretation of the amplified Doppler shifted signal are used to sort the internal carotid artery into one of four categories depending on the estimated percent diameter reduction.

Category I consists of internal carotid arteries suspected of having less than 10 percent diameter reduction. In these, the Doppler signal is considered normal. Category II comprises internal carotid arteries with suspected diameter reductions of between 10 percent and 49 percent. In these, the Doppler signal is harsh and has a bubbly characteristic but is not associated with an increase in the baseline frequency. Category III comprises internal carotid arteries with a suspected diameter reduction of between 50 percent and 99 percent. In these, the Doppler shifted frequency is substantially increased from the baseline. Category IV comprises those internal carotid arteries with suspected total occlusion. No Doppler signal is obtained from such vessels. Arteries with a 50 percent or greater diameter reduction are considered to have a hemodynamically significant stenosis while those with less than 50 percent diameter reduction are not.

Of the 222 arteries studied, 46 subsequently were studied by arteriography and these form the basis of this report. In each instance, four different projections of the carotid bifurcation, in addition to views of the aortic arch and intracranial circulation, were obtained. The percent diameter reduction of the internal carotid artery was determined in the standard manner by a vascular radiologist unaware of the noninvasive study results. The accuracy of the category placement using the ultrasonic arteriograph was assessed by comparing the ultrasonic arteriograph category against the arteriographically determined percent diameter reduction. Sensitivity and specificity of the ultrasonic arteriograph at a 50 percent diameter reduction threshold were also determined.

Results

Overall, 38 of the 46 carotid arteries (83 percent) were correctly categorized by the noninvasive test as follows: 5 of 6 arteries (83 percent) with less than 10 percent diameter reduction, 13 of 17 arteries (71 percent) with a 10 percent to 49 percent diameter reduction, 16 of 18 arteries (88 percent) with a 50 percent to 99 percent diameter reduction and 4 of 5 totally occluded arteries (80 percent). Of the 23 arteries with a lesion producing a 50 percent or greater arteriographic diameter reduction, 22 had been so designated by the ultrasonic arteriograph (sensitivity 96 percent). Likewise, 22 of the 23 arteries that had either no stenosis or one of less than 50 percent reduction as shown by arteriography were correctly identified as such using the ultrasonic arteriograph (specificity 96 percent).

Discussion

The ultrasonic arteriograph has been shown in this study and others[3-5] to have an excellent overall accuracy. It is especially accurate in detecting those lesions which are considered to be hemodynamically significant, that is, within categories III and IV. Combining these two groups yields an accuracy rate of 87 percent for the detection of stenosis with a 50 percent or greater diameter reduction. The accuracy rate in detecting a nonhemodynamically significant stenosis is also acceptable—78 percent, when combining categories I and II. Additionally, the sensitivity and specificity rates, each 96 percent, speak well for the test's ability to differentiate between hemodynamically significant and nonhemodynamically significant disease.

This study compares the results obtained with the ultrasonic arteriograph with those obtained by contrast arteriography. Such a process may lend intrinsic bias to the overall accuracy because in this study those patients in whom contrast arteriography was done were symptomatic and might be expected to have a high incidence of advanced atherosclerosis at the carotid bifurcation. Also, because the accuracy of the ultrasonic arteriograph in the detection of a category I or II stenosis is less than that for detecting a category III or IV stenosis, inclusion of a large number of patients with lesser degrees of stenosis could conceivably decrease the overall diagnostic accuracy. This situation might occur in screening a large population of asymptomatic patients. However, the fact remains that in experienced hands, the ultrasonic arteriograph is highly accurate in the detection of a hemodynamically significant stenosis.

Despite this accuracy, two questions remain: (1) What is the role of identification of an asymptomatic carotid stenosis in stroke prevention and (2) should identification of such a stenosis alter the approach to patient management? In an attempt to answer these questions, the avail-

able data concerning the cause of ischemic stroke and the natural history of the asymptomatic bifurcation stenosis are reviewed.

Ischemic Strokes

Transient ischemic attacks and their potential sequela, ischemic stroke, are generally regarded as embolic in nature. The frequency with which fixed neurological deficits are associated with internal carotid artery occulsion appears to be less than previously considered.[6] Emboli consist of fragments of atherosclerotic plaque or platelet fibrin aggregates that have formed on a previously degenerated plaque (ulcer) and have subsequently been dislodged and carried into the cerebral circulation. As many as 75 percent of such emboli originate in a surgically accessible site in the extracranial cerebral vasculature.[2] Some investigators have suggested that clusters of embolic episodes may occur from an atherosclerotic lesion, with intervals of several years between individual clusters.[7] No hard data are available to support this suggestion.

The prevalence of notable atherosclerotic fibrous plaque at the carotid bifurcation in patients older than 65 years of age examined during autopsy studies approaches 100 percent.[8] In this same age group, complex carotid bifurcation lesions, defined as fibrous plaques with areas of hemorrhage, ulceration, necrosis or thrombosis are found in nearly 40 percent. The reported incidence of complex plaques determined from examination of operative specimens varies widely. Blaisdell and associates[9] noted ulceration at the time of arteriotomy in 80 percent of the arteries with a 30 percent or greater stenosis. On the other hand, Edwards and associates[10] found ulceration in only 40 percent of their operative specimens. Hertzer and associates[11] used scanning electron microscopy of carotid endarterectomy specimens and demonstrated microulceration or thrombus adherent to the vessel wall in eight of ten arteries examined. If atherosclerosis of the carotid bifurcation, either with or without ulceration, was the only determinant of transient ischemic attack and stroke, one would expect the incidence of stroke in the elderly to parallel the incidence of occlusive disease at the bifurcation. However, this incidence is much higher than the current stroke rate estimates of 1 percent per year for this same population.[12] Additional factors, at present poorly defined, must also be operative.

Recent reports have further confused the ulceration issue. Using life-table methods, Moore and co-workers[13] reviewed and classified asymptomatic nonstenotic carotid ulcerations into groups containing either small, large or complex ulcerations. Carotid bifurcation endarterectomy was recommended for the combined large and complex ulcer groups based on an observed average annual stroke rate of 12.5 percent. Observation was recommended for the small bifurcation ulcer group based on an average annual stroke rate of 0.4 percent. On the other hand, Kroener and colleagues,[14] using a similar classification and life-table analysis in a similar group of patients, could find no difference in ischemic neurological events between large and small ulcers or between those ulcers associated with a stenotic and those associated with a nonstenotic lesion. Their cumulative seven-year stroke rate was only 1 percent. Unfortunately, of the currently available noninvasive tests, including the ultrasonic arteriograph, none are capable of routinely detecting ulceration.

Independent reports by Thompson[15] and Humphries[16] gave divergent recommendations for the management of asymptomatic bifurcation stenosis based on the observed natural history in their patients. Thompson[15] found a 27 percent incidence of transient ischemic attacks and a 15 percent incidence of stroke without antecedent symptoms in a group of 138 patients with mid-cervical bruits who were not subjected to endarterectomy. Mean follow-up time was 45 months. They concluded that prophylactic endarterectomy was indicated for the asymptomatic stenosis. Unfortunately, arteriograms were obtained in only slightly more than half of the patients, and correlation of the location of the bruit with the type and site of the neurological event was not explicitly stated. In this series, the decision not to operate was made because of overriding associated medical conditions, the nature of the bruit, or the referring physician's or the patient's reluctance to proceed with an operation. Humphries[16] followed 168 patients with asymptomatic stenosis of greater than 50 percent a mean of 32 months. He reported a 15.5 percent incidence of transient ischemic attacks and a 0.5 percent incidence of stroke without antecedent symptoms and concluded that such patients should be followed rather than undergo an endarterectomy. In contrast to Thompson's series, Humphries' series contained a high proportion of patients in whom an endarterectomy had been done previously on the contralateral artery. Such a difference may be important as it has been

suggested that correction of a stenosis on one side may mitigate coexistent contralateral disease.[17]

Perioperative stroke remains a devastating complication of many otherwise successful major operative procedures. Some surgeons advise prophylactic endarterectomy for an asymptomatic carotid stenosis in patients about to undergo other major vascular, thoracic or cardiac procedures. The available data do not support this approach. Reports by Carney and co-workers,[18] Evans and Cooperman,[19] and Treiman and colleagues[20] have shown virtually identical perioperative stroke rates in patients with asymptomatic stenosis or bruits as compared with those without these findings. If anything, there are slightly more neurological events in those without bruit or documented stenosis. Recognition that an asymptomatic carotid stenosis is but one manifestation of a generalized process—atherosclerosis—should heighten the awareness of the health care team that a patient with such a lesion may be at an increased risk during the perioperative period for cerebrovascular and cardiovascular complications and should permit institution of additional precautionary and prophylactic measures to minimize the possibility of such complications from occurring.

With these opposing opinions on the natural history and the divergent recommendations for treatment of asymptomatic carotid bifurcation disease, the question remains: Where does noninvasive testing in general and ultrasonic arteriography in particular fit into the scheme of patient management? The following recommendations seem prudent.

Patient Management

First, as a diagnostic procedure ultrasonic arteriography is not indicated in patients with classic hemispheric transient ischemic attacks or resolved stroke. Arch and four-vessel arteriography with intracranial views are mandatory to define the anatomy and to plan an operative approach in such patients. Yet this group of patients provides a large pool of arteriogrammed arteries against which the findings of the ultrasonic arteriograph might be compared for determining individual laboratory accuracy rates and for ongoing quality assurance. It is only in this regard that ultrasonic arteriography can be recommended in patients with classic hemispheric ischemic symptoms. As such, it would be inappropriate to charge these patients for such examinations.

Second, patients scheduled for major abdominal, thoracic, vascular or cardiac operations in whom a midcervical bruit is discovered should undergo preoperative ultrasonic arteriography. This should be done to identify the origin of the bruit and heighten the awareness of the health care team to the possibility of increased risk of cardiovascular and cerebrovascular complications. It should not be used to identify patients for prophylactic endarterectomy before the planned procedure, as the efficacy of such a therapeutic approach has not been documented.

Third, evidence that prophylactic endarterectomy in asymptomatic patients alters their subsequent stroke risk is not convincing. Until the natural history of the asymptomatic carotid stenosis is better defined, the use of ultrasonic arteriography to identify asymptomatic patients for prophylactic endarterectomy cannot be justified. However, it might be useful in selecting that group of patients who may have an increased risk of neurological events. Such patients should receive intensive education about the signs and symptoms of transient ischemic attack and stroke and instruction to report promptly to their physicians the development of such findings. Perhaps this approach could decrease the annual stroke rate. However, as there is evidence that the stroke rate has been declining in recent years, this would be hard to document. A consensus on which patients should be included in a high-risk group will be difficult to reach, but it should probably include those with ultrasonic arteriographic evidence of high-grade bifurcation stenosis and those with evidence of unilateral total occlusion of the internal carotid artery.

Finally, in those patients with atypical symptoms that may represent ischemic neurological events, ultrasonic arteriography should be done. Should a significant stenotic lesion be identified, endarterectomy could then be offered, recognizing that only about 15 percent of patients with atypical symptoms will be relieved of their symptoms following the procedure. With additional experience, it may be possible to use the findings of ultrasonic arteriography to help select for endarterectomy that group of patients with atypical symptoms who are most likely to obtain relief of symptoms.

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Mechanism of Mitral Valve

I THINK WE DO an injustice to the mitral valve in saying that if the mitral valve closes one leaflet a little bit above the other and a click or noise is produced, that it's necessarily abnormal. I find it hard to believe that up to 20 percent of the young female population is abnormal. And so I think to a large extent we're calling normal "abnormal." I agree that some people do get in trouble, and they may have increased rhythm disturbances, but generally speaking those are the people who have multiple clicks or midsystolic clicks or late-systolic murmurs. But the person who has just a little asymmetric closure on an echocardiogram and have a very early click—I have the feeling that's within normal limits.

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Intestinal Protozoan Infections: Prevalence in the San Francisco Bay Area

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A sample of 415 members of the Kaiser Foundation Health Plan (KFHP) were tested for intestinal protozoa. This parasite survey group was found to be comparable in age distribution, sex and ethnic background with the membership at large. Gastrointestinal complaints were no more numerous in this group than in a large series of KFHP members taking multiphasic examinations. Because KFPH membership included, at the time of the survey, approximately 27 percent of all residents of the San Francisco Bay Area, the membership may be considered approximately representative of the entire area. Fourteen percent of persons were found to be infected with one or more intestinal protozoan parasites, while 5.5 percent harbored potentially pathogenic sorts. Entamoeba histolytica *was found in 0.7 percent of those surveyed,* Giardia lamblia *in 1.7 percent and* Dientamoeba fragilis *in 3.1 percent.*

THE TRUE PREVALENCE of intestinal parasitic infections in the United States is completely unknown. Brooke[1] estimated the prevalence of amebiasis to be 5 percent—a figure considered a rough estimate in 1964 and now certainly out of date. More recent epidemiologic studies, such as that of Krogstad and associates,[2] confirm the presence of foci of endemic amebiasis but do not attempt to estimate prevalence. Limited surveys, such as those of Spencer and co-workers[3] and of Lynch and Harmon,[4] undertaken in areas where such infections were thought to be prevalent, have produced figures of little general applicability. Prevalence rates for *Giardia* and *Dientamoeba* are likewise unknown.

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Estimates based on routine stool examinations must be interpreted with caution. Specimens are generally derived from a selected group, presumably more symptomatic and, thus, more likely to be infected than the general population. Additional factors of major importance influencing the results are (1) the manner in which specimens are collected, processed and examined, (2) the technical competence of the laboratory personnel and (3) the index of suspicion for intestinal parasitic infections by the physicians who traditionally initiate the testing process. We report here an attempt to control these factors and to determine the approximate prevalence of intestinal protozoan infections in a group roughly representative of the general population of the San Francisco Bay Area.

Patients

Asymptomatic persons, who have no reason to suspect that they might be infected, are not easily persuaded to submit stool specimens for examina-

ABBREVIATIONS USED IN TEXT

KFHP = Kaiser Foundation Health Plan
MHC = multiphasic health checkup
PVA = polyvinyl alcohol

tion. However, we were able to secure such a group from among members of the Kaiser Foundation Health Plan (KFHP) having multiphasic health checkups (MHC's) in Oakland, California. The MHC consists of a detailed health questionnaire that includes a review of symptoms checklist, filled out in advance by the patient, and a series of laboratory, x-ray and electrocardiographic studies, all of which are completed before a physical examination is done by a physician or nurse practitioner. The MHC is primarily intended as a periodic screening examination for presumably well persons 15 years of age or older. About 25,000 MHC's are done annually at our Oakland facility, and most of those taking the examination come from the cities of Oakland and Berkeley.

Methods

On several randomly chosen dates in 1978 and 1979, persons taking the MHC were offered the option of stool examinations for parasites and were given the explanation that such infections could be asymptomatic. Those who decided to avail themselves of our offer (about half the total number of persons examined on each day) were given kits containing two vials of polyvinyl alcohol (PVA) preservative solution. An accompanying instruction sheet provided them with details of collection and preservation, which specified that the specimens should be added to the preservative immediately after passage and that specimens should be collected on two separate days. The 415 persons who brought in both specimens (the parasite survey group) provide the basis for this report. Slides were prepared from each stool specimen and stained by the Wheatley[5] modification of Gomori's trichrome staining method. They were then examined by one of the authors and in any questionable instances by both.*

Results

Table 1 shows the results of these examinations with 99 percent confidence limits[6,7] for the values given. No patient in this series was found to have more than one pathogen.

In March 1980 approximately 11 percent of the KFHP membership for Northern California lived in the Oakland and Berkeley area. Table 2 compares the ages of those among the 156,858 members from this area who are 15 years of age or older with those of persons surveyed for intestinal parasites, as well as the level of infection found in all ages of the latter group. Although those taking the MHC were of a somewhat older mean age than the general health plan membership, levels of infection (except in the 20- to 29-year-old age group) were relatively constant up to the age of 70 years.

A sample of 4,000 patients who had MHC examinations in Oakland and San Francisco in December 1976 was analyzed by sex and ethnic grouping (Arthur L. Klatsky, MD, Permanente Medical Group, Oakland, California, personal communication, October 1980). Table 3 compares the parasite survey group with this sample.

TABLE 1.—*Prevalence of Intestinal Protozoa in 415 Multiphasic Health Checkup Patients**

Parasite	*Percent Infected*	*99 Percent Confidence Limits*
Any	14.22	10.1-19.2
Potential pathogen	5.54	3.1- 9.1
Entamoeba histolytica	0.72	0.1- 2.6
E hartmanni	1.93	0.6- 4.4
E coli	3.61	1.7- 6.7
Endolimax nana	6.51	3.8-10.3
Iodamoeba bütschlii	1.20	0.3- 3.4
Dientamoeba fragilis	3.13	1.4- 6.1
Giardia lamblia	1.69	0.5- 4.1
Chilomastix mesnili	0.48	†0.0- 2.2

*Members of the Kaiser Foundation Health Plan who made up the parasite survey group.
†Expressed as nearest 0.1 percent.

TABLE 2.—*Comparative Age Distribution, Oakland-Berkeley Kaiser Foundation Health Plan Members and MHC Parasite Survey Group*

	Percent		
Age (yrs)	*Health Plan Members**	*Parasite Survey Group†*	*Infected‡*
15-19	8.88	0.5	0.0
20-29	18.97	10.0	20.0
30-39	19.58	22.0	14.4
40-49	10.27	15.0	14.3
50-59	9.69	25.5	15.0
60-69	6.76	20.0	15.8
70-79	3.18	8.5	5.7
80+	1.10	1.0	0.0

MHC = multiphasic health checkup

*March 1980: 156,858 members in Oakland-Berkeley area.
†Expressed to nearest 0.5 percent.
‡Parasite survey group, any parasite.

*Assistance was also provided by Patricia Quinn, BA, a senior laboratory technologist, who occasionally reviewed slides in which there was some question of identification.

Sex distribution was almost identical in the two groups. Ethnic groupings did not correspond as closely, perhaps because lack of time and other constraints did not allow us to verify the ethnic origin of many persons whose race could not be determined from their charts (arbitrarily designated within the ethnic category "other" in our summary) or whose charts were unobtainable for review.

We noted little difference in the prevalence of parasites among the ethnic groups (Table 4), with the exception of those of Hispanic origin. Ethnic grouping was on the basis of the patient's own assessment; those indicating Hispanic origin (a small percentage in both series) generally had close ties with Mexico. It should also be noted that the Asian category in the health plan population did not, at the time of this survey, include appreciable numbers of Southeast Asian refugees.

We were aware that the offer of stool examinations might attract a disproportionate number of those persons taking the MHC who had gastrointestinal complaints. Thirteen percent of persons in the parasite survey group listed, on the review of symptoms checklist, one or more current complaints suggesting gastrointestinal disease. Data have been compiled (Abraham B. Siegelaub, MS, Kaiser-Permanente Medical Care Program, Oakland, California, personal communication, March 1981) from the answers given by nearly 111,000 persons to a similar but more comprehensive questionnaire used in the MHC during the years 1964 through 1968, which show that the parasite survey group had fewer gastrointestinal complaints than were expressed by the 1964-1968 group.

TABLE 3.—*Comparative Distribution by Sex and Ethnic Group,* MHC Sample† and Parasite Survey Group‡*

	Percent	
	MHC Sample	*Parasite Survey Group*
Male	46.0	45.8
Female	54.0	54.2
Asian	6.0	11.3
Black	27.0	26.8
Hispanic	2.6	3.1
White	61.0	48.4
Other	3.4	11.4*

MHC = multiphasic health checkup

*Including those persons for whom this information unavailable.
†4,000 patients who had MHC's in Oakland or San Francisco, December 1976.
‡415 patients from Kaiser Foundation Health Plan.

TABLE 4.—*Prevalence of Infection* in Parasite Survey Group† by Ethnic Distribution*

Ethnic Groups	*Distribution (percent)*
Asian	10.6
Black	10.0
Hispanic	30.8
White	14.4

*Any parasite.
†415 patients from Kaiser Foundation Health Plan.

Discussion

Although *Entamoeba histolytica* was found in less than 1 percent of those surveyed, the combined *E histolytica-E hartmanni* prevalence was 2.65 percent. Until relatively recently, the nonpathogenic *E hartmanni* was not always differentiated from *E histolytica*. Of the three potential pathogens found in 5.5 percent of those surveyed, *Dientamoeba fragilis* was the most common. Yang and Scholten[8] found that *D fragilis* caused symptoms in approximately 25 percent of a series of patients infected with this parasite only. Others have given figures as low as 15 percent of symptomatic infections. This somewhat labile parasite is not frequently reported; its apparent rarity is probably a result of improper handling of stool specimens. *D fragilis* is more readily identified from specimens examined immediately after they are passed or preserved at that time in PVA fixative[9]; it is not found in specimens examined by means of a concentration technique only.

The examination of additional stool specimens from each of our patients (which did not seem feasible) would almost certainly have resulted in higher percentages of parasites isolated, and the figures given may thus be considered lower limits for the true prevalence of these parasites in the area investigated.

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Modern Neurosyphilis: A Partially Treated Chronic Meningitis

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Approximately 5,000 new cases of neurosyphilis may occur in the United States each year. General paresis and tabes dorsalis, however, have become relatively rare since the introduction of penicillin. Seizures, neuro-ophthalmologic symptoms, stroke and acute meningoencephalitis are currently the most common manifestations of neurosyphilis.

In more than a third of patients with neurosyphilis, nontreponemal tests for syphilis (such as VDRL) are negative and should not be used to exclude the diagnosis. Specific treponemal tests are more sensitive and more specific. Examination of the cerebrospinal fluid may show no abnormalities in neurosyphilis and is not an infallible guide to the activity of the infection.

Penicillin is the only proven antibiotic treatment of neurosyphilis. However, low-dose regimens do not produce spirocheticidal concentrations in the brain, and high-dose penicillin therapy is recommended to insure eradication of the spirochetes. Doxycycline, a tetracycline derivation that achieves relatively high concentration in the brain, may also be effective.

MEDICAL STUDENTS AND PHYSICIANS in training should be challenged by the statement that "Neurosyphilis is not rare, but you will probably fail to recognize your first case of this treatable disorder." Although penicillin has clearly reduced the frequency of the disease, the expectation that it would eradicate neurosyphilis remains unfulfilled. At the same time, formal training in recognizing the variable manifestations of the infection has waned in medical schools, almost to the point of considering neurosyphilis of only historical importance.

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The true incidence of this disease is unknown. However, approximately 50 new cases of neurosyphilis are diagnosed each year in those medical centers where personnel have more experience in recognizing or suspecting this disease.[1,2] In addition, over 50,000 new cases of syphilis are thought to go undetected each year in the United States, and the number of untreated patients with any form of syphilis has been estimated at 510,000.[3-6] This venereal disease is particularly prevalent in large urban areas and within homosexual communities. Assuming that in 10 percent of patients with an untreated form of syphilis, neurosyphilis[7] will develop, then more than 5,000 new cases may occur each year. Clearly, then neurosyphilis still

ABBREVIATIONS USED IN TEXT

AR = Argyll Robertson (pupil)
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption (test)
MHA-TP = microhemagglutination test for *Treponema pallidum*

exists. Its accurate diagnosis, however, requires particular astuteness. The clinical manifestations are extremely variable and may have changed in the postantibiotic era, so that the classic findings of neurosyphilis are often absent.[1,2] Also, routine screening serological tests for syphilis do not detect a third or more of the cases of active neurosyphilis, and specific treponemal tests must be used to exclude the disorder.[8-10] Past penicillin treatment also does not exclude the possibility of active syphilis because some recommended penicillin regimens do not produce spirocheticidal levels in the brain.[11]

To increase the awareness of these and other observations, the present review of modern neurosyphilis was undertaken. The focus of the report is on adults who have *acquired* the treponemal infection. Although many of the comments also pertain to congenital neurosyphilis it is not separately reviewed.

Historical Background and Classification

The recent history of neurosyphilis began in 1905 when the spirochete *Treponema pallidum* was first described by Schaudinn and Hoffman. A year later Wasserman's complement-fixation test was developed and permitted the serological confirmation of syphilis in patients with neurological disorders. In 1913, Noguchi and Moore found treponemes in the brains of patients with general paresis, providing final proof for the long-proposed postulate that syphilis could infect the brain (see ref. 12 for review).

During this preantibiotic period it was well known that syphillis began with an epithelial lesion that was characterized by a painless, and often ulcerated, papule; this chancre appeared ten days to several weeks after sexual transmission. Serological tests remained negative for one to three weeks but became positive after six to eight weeks—and preceding the variable systemic and mucocutaneous manifestations of disseminated secondary syphilis.[12]

The spirochetes invaded the central nervous system either during the secondary phase of the disease or within two years of the primary infection in 35 percent to 45 percent of untreated cases.[7] The initial mode of infection was a form of meningitis, which varied from an asymptomatic illness to a syndrome with headache, nuchal rigidity and, at times, confusion, cranial nerve palsies, convulsions, increased intracranial pressure and hydrocephalus. Examination of spinal fluid showed a pleocytosis that was predominantly lymphocytic.

The initial meningeal infection, if untreated, either remitted spontaneously or evolved into a chronic, initially asymptomatic, meningitis.[7] This persistent meningitis produced a variable, although largely predictable, sequence of pathological findings that formed the basis of most classifications of neurosyphilis (Table 1).

In the chronic form of syphilitic meningitis pathological findings consisted of diffuse or discrete (for example, gummatous) collections of lymphocytes, plasmacytes and occasional polymorphonuclear leukocytes in the meningeal spaces, with an associated adhesive fibrosing arachnoiditis. However, with time an endarteritis involving large or medium-sized cerebral and meningeal vessels also developed. These vessels became infiltrated by spirochetes and inflammatory cells leading to fibroblastic thickening, cerebrovascular occlusion and stroke (that is, meningovascular syphilis). This endarteritis usually became symptomatic six to ten years after the primary infection but could occur as early as six months or as late as 15 years.

If the chronic fibrosing meningitis bypassed or persisted asymptomatically beyond the meningovascular stage, then parenchymal damage occurred by direct parenchymal invasion of the spirochetes. This parenchymal infection commonly became symptomatic 15 to 20 years after the primary infection. When *T pallidum* maximally infected the cerebral cortex, a meningoencephalitis developed which, if untreated, resulted in irreversible neuronal loss, demyelination and gliosis in the brain. While dementia or behavior change was the initial symptom, the name general paresis was applied to this chronic meningoencephalitis because as the disease progressed, various debilitating complications severely limited activity. Another common area of parenchymal involvement included an admixture of pupillomotor structures and the dorsal roots and columns of the spinal cord that produced a syndrome called tabes dorsalis. Similarly, relatively selective injury of the optic nerves produced loss of vision and optic atrophy; spirochetal

TABLE 1.—*Historical Classification of Neurosyphilis**

Clinical	*Pathological*	*Onset After Primary Infection*†
Asymptomatic	Chronic meningitis	2 mo-15 yr
Meningeal	Meningitis with or without cranial neuropathy, hydrocephalus	2 mo-2 yr
Meningovascular	Chronic meningitis with:	6-10 yr
Cerebral	Endarteritis and cerebral infarction	
Spinal	Infarction of the spinal cord	
Parenchymal	Chronic meningitis with:	10-20 yr
General paresis	Chronic encepahlitis	
Tabes dorsalis	Spinal root and cord atrophy	
Optic atrophy	Optic atrophy	
Spinal	Myelitis	
Gumma formation	Syphilitic granuloma, usually in proximity to meninges	Variable
Congenital syphilis	Includes all of the above	Newborn to adolescence

*Adapted from Refs. 7 and 12.
†Most frequent time of onset but variable.

invasion of the spinal cord resulted in a meningomyelitis with a spastic paraparesis or quadriparesis.

In a given person one neuroanatomic site often appeared to be selectively involved. However, after progression of the infection, pathological and clinical studies usually showed a great deal of overlap between the different forms of parenchymal neurosyphilis, and even between modes of neural injury. In a single patient parenchymal damage could be due to a combination of spirochetal invasion, a syphilitic endarteritis and a fibrosing arachnoiditis.[7,12]

Modern Neurosyphilis

The initiation of penicillin therapy in the 1940's radically altered neurosyphilis. While previous forms of treatment such as bismuth, arsenic and malarial therapy were felt to be partially beneficial, penicillin was treponemicidal and effectively treated all forms of syphilis. The result was a substantial decrease in the frequency of new cases of classic neurosyphilis. However, neurosyphilis was not eradicated by the antibiotic era. Instead, its natural history and clinical manifestations were modified, and it became more monosymptomatic and often more subtle.[1,2,13] It is thought that the widespread use of antibiotics given by mouth, such as penicillin, ampicillin and tetracycline, for various infections has inadvertently changed neurosyphilis into a progressive, *partially treated, chronic meningitis.* As a result, partial rather than fully developed manifestations are the rule.

This proposal is supported by comparing the clinical presentation of neurosyphilis reported to have occurred in Boston from 1932 to 1942[7] with a composite of cases recently reported in the postantibiotic era.[1,2,11,14-26] A total of 610 cases of neurosyphilis reported since 1965 were reviewed, and 324 that met accepted criteria for the diagnosis were selected. The diagnostic criteria for neurosyphilis included the following: (1) Neurological or ophthalmologic symptoms (or both), with positive serological tests for syphilis and abnormal results of a CSF examination (for example, more than five leukocytes per cu mm, elevated protein, elevated gamma globulin, abnormal colloidal gold test, or positive serological tests for syphilis) *or* (2) asymptomatic condition with serological evidence of syphilis and more than five leukocytes per cu mm in the CSF.

Cases of proposed seronegative neurosyphilis with normal CSF findings were excluded. These 324 cases, plus 11 patients personally seen over three to four years, demonstrated a change in the symptomatic presentation of neurosyphilis in the postantibiotic era (Table 2).

General paresis and tabes dorsalis, which were the most common forms of neurosyphilis in the 1930's are now less frequent presenting problems. Instead, seizures and neuro-ophthalmologic symptoms have become prominent manifestations.

Syphilitic Seizures

Following the introduction of serological tests for the verification of syphilis, seizures were considered to be a minor manifestation of neurosyphilis.[7] Convulsions were not part of the tabetic syndrome. Seizures were thought to complicate general paresis only late in the course of illness, and if the paretic patient was treated before their onset, it was unlikely that convulsions would

occur. Seizures were noted, however, in approximately a fifth of the patients with meningovascular syphilis.[7,27] These observations indicate that before the antibiotic era, seizures were an early manifestation in less than 5 percent of patients with symptomatic neurosyphilis. In comparison, seizures are now prominent in more than 25 percent of symptomatic cases (Table 2). Part of the increased frequency may be due to an inclusion of patients in whom the initial manifestation of meningovascular syphilis was seizures. However, a third of the patients with syphilitic seizures were otherwise asymptomatic, indicating that in some, seizures may be the sole manifestation of neurosyphilis.[1]

Syphilitic seizures occur as either partial (such as focal) seizures or partial seizures with secondary generalization. Both a careful history, including observations from a witness of the convulsion, and an electroencephalographic examination may be required to determine the focal initiation of the seizure. More than half of these patients also have abnormal findings on neurological examination, including evidence of a hemiparesis, impaired mentation, pupillary abnormalities, or decreased sensation and muscle stretch reflexes. However, as noted above, a third of the patients have no clinical findings to suggest a cause for their seizures. Therefore a *treponemal* serological test (see below) should be obtained in every adult with the onset of partial seizures of unknown cause.

Neuro-ophthalmologic Findings

Disorders of the visual fields and acuity, ocular motility and pupillary function are frequent manifestations of neurosyphilis. Syphilitic involvement of the optic nerve produces either a slowly progressive loss of vision due to a parenchymal optic atrophy or a rapid reduction from an acute optic neuritis.[28] The progressive optic atrophy usually occurs over months to years and if untreated will produce blindness in most patients within five years.[28,29] While the nerve degeneration can be segmental, it usually begins peripherally, adjacent to infected meninges, and then proceeds to the center of the nerve. Therefore, a progressive concentric constriction of the peripheral visual fields is a characteristic finding. Although visual acuity is frequently decreased, syphilis can produce a pronounced contraction of the visual field with retention of normal vision. Funduscopic examination shows a retrograde optic nerve axonal degeneration. There is a loss of retinal fibers that produces a sharply demarcated optic disc with reduction of the number of small capillaries at the disc margins but preservation of the central retinal vessels. The symptoms of syphilitic optic atrophy may involve primarily one eye; however, the visual fields and funduscopic findings usually involve both.

TABLE 2.—*Comparison of Clinical Presentation of Neurosyphilis in Boston Study With Composite of Cases in Postantibiotic Era*

	*1932-1942**		*1965-1980†*	
Clinical Problem	*No. Patients*	*Percent*	*No. Patients*	*Percent*
Symptomatic				
Seizures	4	1	59	28
Neuro-ophthalmologic	20	4	56	26
Meningovascular	103	18	42	20
Dementia (paresis)	203	35	26	12
Acute or chronic myelopathy	19	4	10	5
Tabes dorsalis	203	35	9	4
Cranial nerve VIII	9	2	4	2
Miscellaneous	6	1	6	3
	563	100	212	100
Asymptomatic	219		123	
TOTAL	782		335	

*Boston study; the figures for paresis were increased to equal tabes as suggested by Merritt et al.[7]
†Composite of cases, adapted from references 1, 2, 11, 14-26.

Whereas the progressive optic atrophy is a form of late parenchymal neurosyphilis, the acute optic neuritis may accompany an early syphilitic meningitis or even occur during the secondary stage of disseminated syphilis. Vision is rapidly reduced, often reaching a maximum density in the first week. Only one eye is usually involved and pain in that eye may precede or accompany the loss of vision. Visual field defects are extremely variable, but, in contrast to syphilitic optic atrophy, the acute neuritis frequently produces a central or paracentral scotoma. Funduscopic examination may show edema of the optic disc or remain normal in cases of retrobulbar syphilitic optic neuritis.[28]

Besides damaging the optic nerve, syphilis can impair vision by infection of the retina and choroid (chorioretinitis), usually in the region of the optic disc or posterior pole of the eye, or by inflammation and opacification of the cornea (keratitis).[28]

Disorders of eye movements are usually due to inflammation and fibrosis of the third, fourth and sixth cranial nerves as they lie within the meningeal spaces. The oculomotor or third cranial nerve

is most commonly involved and may be the only manifestation of neurosyphilis.[21,28] The clinical appearance of a third nerve paresis is so well known that it will not be described beyond stating that an enlarged pupil that is poorly reactive may precede ptosis or eye muscle weakness. This is because the pupillomotor fibers are situated in the periphery of the third nerve, which is also the site of early inflammation and fibrosis in a chronic meningitis.[30]

A more specific pupillary sign of neurosyphilis is a dissociated response to light and convergence in an eye with preserved vision. The pupil reacts poorly to light but well to convergence. Douglas Argyll Robertson in 1869 noted that this light-convergence dissociation was accompanied by miosis and a poor response to mydriatics in tabes dorsalis. While the Argyll Robertson (AR) pupil is usually irregular and bilateral, most neurologists require only the light-convergence dissociation and miosis for its identification. The AR pupil has always been considered and remains *almost* pathognomonic of neurosyphilis (see ref. 31 for the authoritative discussion). However, when a pupil with a light-convergence dissociation is not miotic, a variety of neurological disorders including syphilis may be present.[4,31] Therefore, a clear definition of miosis is needed to identify an AR pupil. In an adult, a pupil 2 to 3 mm or smaller in diameter *in darkness* is miotic. Under the bright light of an examining room, a pupil of 2 to 3 mm may reflect a normal physiological response. However, the same pupil in darkness dilates to 6.0 to 8.5 mm in persons younger than 45 years of age—an AR pupil does not.[31]

The cause of an AR pupil has remained controversial for more than 100 years. Suffice it to say that some neuro-ophthalmologists consider syphilitic involvement of the rostral midbrain most likely, while others think the ciliary ganglion and nerves may be involved.[14,28]

Meningovascular Syphilis

Meningovascular neurosyphilis denotes syphilitic processes of both the meninges and cerebral vasculature. The location and intensity of infection may be quite diverse and produce polymorphic clinical manifestations. In general, a stroke, an acute meningoencephalitis or an admixture of both are the presenting problems. There may be an acute onset of a hemiparesis, homonymous hemianopia or aphasia, indicating a focal area of cerebral ischemia. These signs, however, can be accompanied or overshadowed by a disoriented, confusional state and a cerebrospinal fluid (CSF) pleocytosis. Convulsions may occur and clinical signs of a meningeal inflammation may be prominent or absent. Meningovascular syphilis, therefore, should not be considered only as a treatable cause of stroke, but also entertained in cases of meningitis of an unknown cause and proposed viral meningoencephalitis.

Meningovascular syphilis usually occurs within ten years of the primary infection and, frequently, in patients 30 to 45 years of age. Therefore, in a young patient with a stroke a diagnosis of syphilitic endarteritis is actively pursued. In an older patient with a stroke, syphilis is at times unenthusiastically investigated because in the vast majority of cases the stroke is due to a nonsyphilitic thrombosis or embolus. However, meningovascular syphilis does occur after age 65, and to exclude it as a cause of stroke simply on the basis of age is an error.

Dementia (General Paresis)

Although less infrequent, syphilis remains a potentially treatable form of dementia. The presenting symptoms of a chronic syphilitic meningoencephalitis do not differ from less treatable forms of presenile dementia. The first symptoms are insidious in onset and consist of defects in memory, concentration, judgment and calculations. There are often associated behavioral changes such as apathy, deterioration in personal hygiene, emotional lability and, on occasion, delusional ideation and hallucinations. As the disease progresses these initial symptoms intensify. The patient eventually reaches a point of such debilitation (or paresis) that he or she is restricted to bed.

A chronic meningoencephalitis may not be the only pathological cause of a syphilitic dementia. A syphilitic meningitis may impede CSF flow and produce a communicating hydrocephalus that is readily treatable by a CSF shunting procedure.[32] Communicating hydrocephalus should be considered in every case of syphilis-induced dementia that does not respond to optimal antibiotic treatment.

Tabes Dorsalis

The term tabes signifies progressive wasting and emaciation and was initially used to describe patients with chronic spinal paralysis of various causes. However, with time tabes came to indicate a syndrome of spinal syphilis characterized by lightning pains, AR pupils, absence of muscle

stretch reflexes and ataxia.[12] Sensory complaints are early and often predominant symptoms. Lancinating pains occurring in attacks that last minutes to days happen in 90 percent or more of cases. These pains are associated with an inflammatory sensory radiculopathy that results in atrophy and fibrosis of multiple nerve roots.

During the initial evaluation of patients with tabetic sensory symptoms, AR pupils, bilateral ptosis and diminished vibration, proprioception, deep pain sensation and two-point discrimination are often found. Difficulty with urination and sexual impotence are common complaints. Once established, the disease slowly progresses over 10 to 20 years and ataxia becomes increasingly prominent and disabling. This sensory ataxia is due to a loss of proprioception in the legs, and reflects the prominent atrophy of the dorsal roots and columns of the spinal cord.[12]

Other Manifestations

Syphilis may also involve the spinal cord by direct parenchymal invasion or indirectly through meningovascular inflammation and vascular occlusion with secondary infarction. Onset of symptoms may be abrupt or gradual and the course may be progressive. Paraparesis or quadriparesis, sensory loss in the extremities, incontinence and hyperreflexia are the usual signs. They may lead to a diagnosis of multiple sclerosis or transverse myelitis, neither of which has a specific treatment. It cannot be stressed strongly enough that *neurosyphilis can mimic every clinical and laboratory manifestation of multiple sclerosis* including disseminated lesions throughout the central nervous system, with remissions and exacerbations. I am personally aware of a 26-year-old woman with a syndrome of progressive myelopathy and optic atrophy, mild pleocytosis and elevated gamma globulin levels in the CSF, and negative serum and CSF *nontreponemal* serological tests. A diagnosis of multiple sclerosis was made and a specific treponemal serological test was never obtained. Postmortem examination demonstrated spinal neurosyphilis.

Other less common manifestations of syphilis include dizziness, hearing loss, psychotic behavior, spinal arachnoiditis, circumscribed gumma formation acting as a mass lesion, atypical neuritic pains, isolated cranial neuropathies and progressive muscular atrophy. These problems will not be considered in detail except to stress that syphilis should be considered in most progressive neurological disorders before a diagnosis of untreated degenerative disease is accepted.

Asymptomatic Neurosyphilis

An asymptomatic chronic meningeal infection has accounted for approximately a third of all syphilitic infections involving the nervous system in both the preantibiotic and postantibiotic eras. Patients often have been identified because of serological test findings following a general medical screening examination or because of an incidental pupillary abnormality discovered during a routine ophthalomologic examination. It is particularly important to detect and treat such patients to prevent late disabling symptomatic neurosyphilis. An asymptomatic syphilitic meningitis usually develops within a year of the primary infection.[7] Therefore, it is essential that the CSF is examined in every patient infected with syphilis for a year or more or for an unknown duration. In addition, the British recommend that every patient treated for primary and secondary syphilis should have a CSF examination a year after treatment to verify a cure.[33]

Serological and CSF Test Findings

Serological tests used to identify a treponemal infection are either nontreponemal or treponemal. Nontreponemal tests consist of complement-fixation or flocculation procedures aimed at detecting a nonspecific globulin complex called reagin. Reagin serological tests for syphilis, such as the Venereal Disease Research Laboratory (VDRL) flocculation test, lack sensitivity and *should not be used to exclude the diagnosis of neurosyphilis.* More than a third to a half of the patients with neurosyphilis have a negative VDRL test in serum and more than a third have a negative VDRL test in CSF.[1,8-10,34] False-positive reactions occur in collagen vascular diseases, after vaccinations and various viral infections and during pregnancy.[35] Therefore, a nontreponemal serological test is neither sensitive nor specific for neurosyphilis.

Treponemal serological tests are based on a specific immune response to *T pallidum.* The serum fluorescent treponemal antibody absorption (FTA-ABS) test, developed by Hunter, Deacon and Meyer in 1964,[36] is the test of choice to confirm the diagnosis of neurosyphilis. The test consists of incubating a patient's serum with a slide coated with dead *T pallidum* organisms. After this incubation, fluorescein-tagged antibody to human gamma globulin is added. Fluorescence of the

treponemes indicates that antitreponemal antibodies are in the patient's serum.

The FTA-ABS test is reactive in the serum of 95 percent to 100 percent of cases of neurosyphilis.[8-10] A negative FTA-ABS test essentially excludes the diagnosis of neurosyphilis and makes examination of the CSF unnecessary. Its false-positive rate is less than 1 percent in celibate nuns and normal controls, though the incidence of biological false-positive tests may be increased by the presence of collagen vascular disorders.[37] Therefore, the FTA-ABS test is both sensitive and relatively specific for detecting a past syphilitic infection.

A second treponemal test, the microhemagglutination test for *T pallidum* (MHA-TP), can complement and may replace the FTA-ABS test in the near future because it is easier to carry out.[38] This test is based on the ability of serum with antitreponeme antibodies to agglutinate erythrocytes previously coated with antigen from *T pallidum*. It has not yet been determined if the selectivity of the MHA-TP test is equal to that of the FTA-ABS test in patients with neurosyphilis.

A reactive serum treponemal test indicates past infection with syphilis, but it does not by itself indicate active neurosyphilis. A patient successfully treated for syphilis may have a reactive FTA-ABS response indefinitely. Therefore, classically, the spinal fluid has been used as a guide to the activity of neurosyphilis.[39] The VDRL currently remains the test indicated for detecting a syphilitic immune response in the CSF; when positive in CSF it is strong evidence for neurosyphilis.[34,40] False-positive tests rarely occur. The CSF may have a reactive VDRL response in the absence of neurosyphilis either by contamination with seropositive blood (due to a traumatic spinal tap or subarachnoid hemorrhage) or due to entry of serum reagin into the CSF in association with meningitis. As noted above, the VDRL test may be nonreactive in a third of patients with a chronic syphilitic meningitis. Though still under investigation, the FTA-ABS test in CSF currently has no place in the practical management of neurosyphilis. It has a false-positive rate as high as 4 percent to 6 percent and may represent only antibodies that have passively entered the CSF from the serum.[41]

Other abnormalities of the CSF that commonly accompany neurosyphilis include elevated protein (50 to 400 mg per dl) level, lymphocytic pleocytosis (up to 200 to 300 cells per cu mm), and an elevated gamma globulin level. The sugar content is usually normal. The colloidal gold test has been largely replaced by an electrophoretic analysis of gamma globulin.

If the CSF is totally normal in a patient with clinical signs of neurosyphilis then some physicians feel the process has "burned out" and there is no need for further treatment. However, this clinical approach is being seriously challenged in patients in the postantibiotic era who may have partially treated neurosyphilis.

Cerebrospinal Fluid Controversy

J. Lawton Smith, professor of neuro-ophthalmology at the University of Miami, states that "the definite majority of patients with parenchymatous neurosyphilis seen in practice today have cerebrospinal fluids that are essentially normal to all customary clinical parameters, and that such patients also more often have non-reactive serum reagin tests (i.e., VDRL) than not."[14]

Recently, the opposite view has also been stated,

> The CSF is an almost infallible guide, probably even more than the clinical symptomatology, in the diagnosis and treatment and prognosis of the disease. If the CSF is negative in a case in which there are symptoms of neurosyphilis, it may be safely concluded that the syphilitic inflammation in the nervous system is burned out and that further progression of the disease probably will not occur. In cases with progressive neurologic symptoms and a completely negative CSF, a postmortem examination usually discloses a nonsyphilitic neurologic disease.[42]

Thus, a controversy exists on whether totally normal CSF findings exclude active neurosyphilis in need of penicillin treatment. While present evidence cannot resolve this controversy for an individual patient, it does indicate, particularly in the postantibiotic era, that the CSF findings are not infallible.

J. H. Stokes, in 1940—before the era of penicillin treatment—felt that 12 percent of patients with "undoubted neurosyphilis" had normal spinal fluid findings.[43] This conclusion was supported by the observation of patients with signs, symptoms and serological findings of neurosyphilis in whom arsenic treatment provoked an increase in CSF protein and pleocytosis in spinal fluid previously thought to be normal.

More recently, an infectivity test has been used to demonstrate the presence of *T pallidum* in CSF having normal laboratory measurements. Because treponemes cannot be cultured in vitro, an in vivo infectivity test using rabbits or primates has been used. Although interpretation of these infectivity tests differs among investigators,[44] an infective *T*

pallidum can be isolated from presumed normal spinal fluid.[20] This evidence suggests that normal CSF findings do not rule out active neurosyphilis, particularly in the present era when patients may have been partially treated inadvertently with antibiotics. Because of this conclusion, it is recommended that an untreated patient with both signs of progressive neurosyphilis and a reactive treponemal serological test be treated with antibiotics irrespective of the CSF findings. In these patients the CSF should be reexamined approximately a week after initiation of treatment to determine if a reactive pleocytosis had been provoked.[43] This finding would help confirm the diagnosis of neurosyphilis, which can be particularly important if a question of retreatment later develops.

Treatment

Penicillin is the only proved antibiotic treatment for neurosyphilis. However, the optimal preparation, dose and duration of treatment remain unknown. Neurologists in general use larger doses of penicillin than venereologists because of an unsatisfactory cure rate with lower doses. Overall, approximately 25 percent of symptomatic patients and 10 percent of asymptomatic patients treated with various low-dose penicillin regimens fail to have a satisfactory response.[45] Manifestations of parenchymal neurosyphilis, such as general paresis, optic atrophy and tabes dorsalis, are particularly notorious for not responding to low-dose penicillin therapy. Because of these problems, recommended penicillin regimes are based on three principles.[46]

1. The accepted spirocheticidal concentration of penicillin in infected tissue is 0.03 units per ml (0.02 μg/ml). Penicillin, however, penetrates the blood brain barrier poorly and CSF levels may only be 2 percent of serum levels. Brain parenchymal levels of penicillin may be even less than CSF levels, a factor of particular importance when treating parenchymal neurosyphilis.

2. Penicillin's bacteriocidal actions occur during the stage of active spirochete multiplication. Therefore, intervals of subspirocheticidal penicillin concentrations should be shorter than the treponeme replication rate (about 30 to 33 hours in early syphilis and probably longer in neurosyphilis).

3. Response to therapy is related to both the total dose and duration of penicillinemia, as well as the extent and duration of parenchymal brain damage. Injury to the brain, either by neuronal loss, demyelination, gliosis or infarction may be permanent. Noncurative doses of penicillin may not halt or prevent parenchymal injury and, thus, permit progressive irreversible brain damage.

Only two penicillin regimens have been shown to comply with the above guidelines. The first consists of 12 million units of aqueous crystalline penicillin G given intravenously each day (2 million units every 4 hours) for 10 to 15 days.[11] Though it requires that the patient be in hospital, this is the best regimen for a symptomatic condition and is clearly indicated in any patient whose neurological examination suggests a major infection of nervous tissue. Patients who have minor findings (such as an isolated AR pupil) or who refuse hospitalization may be treated as outpatients with 1.2 to 2.4 million units per day of procaine penicillin G given intramuscularly in combination with 500 mg every six hours of probenecid given orally.[47] Probenecid increases penicillin levels in both serum and CSF by decreasing renal and CSF excretion.

In patients with predominantly meningovascular syphilis or no symptoms, it may be acceptable to use an outpatient regimen consisting of 20 million units of procaine penicillin G given intramuscularly in divided doses (2.4 million units every other day) over three weeks.[1] Almost all of these nonparenchymal infections appear to be cured by this amount of penicillin even though the reliability of obtaining therapeutic penicillin levels has not been determined.

The above recommendations differ considerably from the 1976 treatment schedules published by the Venereal Disease Control Advisory Committee for the Center for Disease Control. Their recommendation was as follows:

1. Benzathine penicillin G—7.2 million units total: 2.4 million units by intramuscular injection weekly for three successive weeks;

or

2. Aqueous procaine penicillin G—9.0 million units total: 600,000 units by intramuscular injection daily for 15 days.

However, neither of these regimens produces spirocheticidal levels of penicillin in the CSF.[11] In particular, benzathine penicillin G, while convenient for both the patient and physician, should be avoided in neurosyphilis.

Adverse reactions to penicillin occur either in the form of an allergic (urticaria, rash, anaphylaxis) or a Jarisch-Herxheimer reaction. None of these reactions are dose related. Anaphylaxis,

the most serious allergic response, occurs in 0.04 percent of patients with syphilis.[46] Jarisch (1895) and Herxheimer (1902) described a reaction occurring within 24 hours of the first dose of mercury treatment for syphilis that was characterized by both fever and aggravation of syphilitic symptoms and lesions.[48] It has since been found that the Jarisch-Herxheimer reaction can follow any form of treatment. It occurs most commonly in early syphilis and is thought to be caused by the release of products from dead spirochetes. The Jarisch-Herxheimer reaction occurs infrequently with neurosyphilis, being noted in approximately 2 percent of patients with general paresis, and it rarely affects the long-term outcome. However, this reaction is feared in parenchymal infection of the optic or auditory nerves in which acute blindness or deafness may occur. Therefore, some authors recommend a concomitant course of prednisone in patients with these disorders even though it is not of proved benefit.[46]

There is little published evidence, beyond case reports, that antibiotics other than penicillin are effective in the treatment of neurosyphilis. Tetracycline is known to cure early syphilis and doxycycline, a derivative of oxytetracycline, is particularly lipophilic and achieves five times the concentration of tetracycline in the brain.[49,50] Therefore, 300 mg of doxycycline a day given orally in divided doses for 30 days is an acceptable alternative drug for patients with confirmed penicillin allergies.

Erythromycin has also been tried for neurosyphilis because it is effective systemically. However, its penetration into the CSF is poor and its use cannot be recommended here.[51] It is clear that any patient treated with antibiotics other than penicillin needs particularly close follow-up.

Response to Treatment

As noted above, the clinical response to treatment is dependent on both the penicillin regimen selected and the extent and duration of nervous tissue damage. In general, high-dose penicillin therapy should cure a syphilitic infection limited to the meninges and stop the progression, usually with some clinical improvement, of a parenchymal disorder.[1] Patients must be followed closely to verify that the above goals are obtained. Quantitative reagin serological tests (such as the VDRL) are obtained every three months the first year and should show a drop in titer unless already low. CSF cell count, protein levels, VDRL response and gamma globulin levels are examined at 6 and 12 months and, if not totally normal, again at two years. If after three years the patient remains clinically improved and the CSF and serological tests have reverted to normal, then further observation is not needed.[42,52] However, if during that period there is evidence of clinical progression or failure in improvement of laboratory results, retreatment must be considered. It is recommended to retreat with high-dose, intravenously given penicillin G if any of the following exists:

- There is clinical progression and reevaluation does not indicate an alternative neurological explanation. Retreatment in these patients is especially indicated when there is an initial improvement after penicillin treatment, a persistent CSF pleocytosis, or when the initial treatment is suboptimal.
- There is a failure of the CSF cell count to decline to normal at six months.
- Failure of VDRL titers for serum or CSF to decline or a fourfold rise in titer.
- The initial treatment involved a suboptimal penicillin regimen such as benzathine penicillin.

Some authors also consider a rise in CSF levels of gamma globulin an indication of continued infection. Otherwise, an isolated elevation of CSF protein is not an indication for retreatment.

Tabetic sensory symptoms may not respond to penicillin and in themselves are not an indication for retreatment; presumably, they result from the fibrosis and atrophy of dorsal roots and posterior columns rather than the presence of treponemes. The lightning pains can be reduced by the anticonvulsant carbamazepine.[23]

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Peptic Ulcer Disease

The Flowers That Bloom in the Spring

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SLEISENGER:* *At this Grand Rounds Dr. Altman will discuss peptic ulcer disease. He is the Associate Director of the Gastrointestinal Clinic and Director of the course "Introduction to Clinical Medicine" at UCSF.*

DR. ALTMAN:† The first case involves a 46-year-old man, an attorney, with a 15-year history of documented peptic ulcer disease. His recurring episodes were characterized by epigastric gnawing pain, which was relieved by antacids; often they were accompanied by diarrhea. These episodes were not related to major professional difficulties. However, his most recent exacerbation was associated with severe marital stress. He had no history of loss of blood, recurrent vomiting or pancreatitis. His father, also an attorney in San Francisco, has a long history of peptic ulcer disease but still practices law at the age of 83. Results of our patient's physical examination were normal, except for a tender epigastrium. Laboratory data, including fasting serum gastrin level, were also within normal range. He responded very well to a course of cimetidine given orally and is now asymptomatic.

The second case involves a 45-year-old man, a professor of medicine, with a 17-year history of recurring epigastric pain described as boring and burning and made better by food or antacids. His most severe episodes of pain occurred early in the course of the illness, during his internship. Episodes now seem most related to working under the pressure of deadlines, particularly those associated with grant applications. In contrast to our first patient, he has absolutely no difficulties with ulcer symptoms when he has problems at home. And like the first patient, he has had no episodes of bleeding or vomiting and no prior gastric operations. He has never had a gastrointestinal x-ray study done, and he refuses one at this time. The most recent episode began in February 1981. He administered cimetidine to himself for two weeks before seeking medical attention. Results of a physical examination and laboratory data obtained at that time were entirely within normal limits. He is now asymptomatic, having completed an eight-week course of cimetidine. He currently takes cimetidine at bedtime with antacids as needed.

It has been said that a peptic ulcer may be the

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hole in a man's stomach through which he crawls to escape from his wife. It is not clear, however, whether this is the explanation for the fourfold or fivefold increased incidence of peptic ulcer in men versus women in the United States and around the world.

The subtitle of this conference is "The Flowers That Bloom in the Spring." I have been taught from the earliest time in medical school that there is a high incidence of peptic ulcer exacerbations in the spring and in the fall. Indeed, this is reflected in several retrospective studies, which have shown that the greatest incidence of cases occurred in March, October and November.[1] There is no adequate explanation for this. Several investigators have looked at influences of various meteorologic conditions; another possibility may be reflected by Tennyson's description of the springtime, in which he wrote, "In the spring a young man's fancy lightly turns to thoughts of love." The relationship of love and ulcer disease is certainly unclear and perhaps will be reflected in the discussion of certain personality and psychological aspects of ulcer disease.

The overall incidence of duodenal ulcer disease is declining both in this country and around the world. A nationwide survey[2] of hospital admissions, both medical and surgical, for duodenal ulcer disease showed a considerable decline in the last decade. The factors involved in the falling incidence are unknown. One interesting speculation has been that the so-called urbanization of our societies has passed; that is, that the migration from the rural areas into the cities occurred early in this century, and the adverse influence of this is no longer felt. However, this possibility has not been borne out by an examination of the incidence of ulcer disease in the developing or third world countries.

Ironically, the incidence of ulcer disease is declining while our ability to understand, diagnose and treat this condition is improving. The pathogenesis of peptic ulcer disease involves factors of acid and pepsin, decreased mucosal resistance to acid, deficient neutralization of acid, abnormal gastroduodenal motility, certain environmental influences, heredity and genetics, psychosomatic factors and drugs. The old dictum of "no acid, no ulcer," still seems to apply even though a few exceptions to this rule have been found. There are certain normal mechanisms that control gastric acid secretions by influencing the drive on the parietal cells and the sensitivity of the parietal cells to this drive. There are both stimulatory and inhibitory factors affecting this drive.

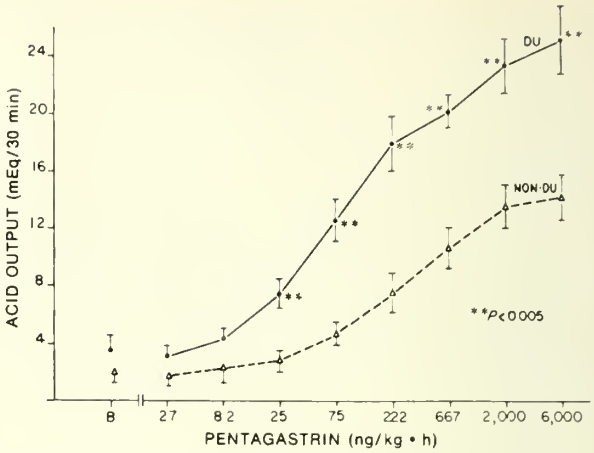

Figure 1.—Mean acid output minus basal output in 20 patients with duodenal ulcers (DU) and 20 non-DU subjects during testing with graded doses of pentagastrin. (Reprinted with permission of Isenberg et al.[3])

In patients with duodenal ulcer disease, there is an increased average peak acid output in response to any of a number of stimuli. There is an increased sensitivity of the gastric parietal cell mass to stimulation by pentagastrin over the entire range of graded doses (Figure 1).[3] It has also been suggested that patients with duodenal ulcer have an increased parietal cell mass compared with a control population. However, there is a large overlap of stimulated gastric acid output among patients with duodenal ulcer, those with gastric ulcer and those without ulcer disease.

Aspects of mucosal resistance to acid are very poorly understood. It has been postulated that certain zones of the stomach and duodenum are particularly susceptible to acid injury by virtue of alterations in their vascularity and other changes in the muscular and vascular interactions in these areas.[4] Ulcers of the esophagus, stomach and duodenum usually occur within two to three cm of mucosal transition zones, suggesting that certain zones of the upper gastrointestinal tract are particularly susceptible to the adverse effects of acid.

Deficient neutralization of gastric acid has also been postulated as a mechanism in the pathogenesis of ulcers. Patients with duodenal ulcer disease have been shown to have a normal output of pancreatic bicarbonate, but this may be inappropriately low considering that they are often "hypersecretors" of acid. Patients who smoke cigarettes have a decreased pancreatic bicarbonate output, and this is directly related to plasma nico-

tine levels.[5] In patients who smoke, the duodenal bulb pH is lower during smoking than it is during a resting period. This may explain the increased incidence of duodenal ulcer in cigarette smokers.

Abnormal motility also may have an effect. Patients with duodenal ulcer may have decreased retrograde peristalsis in the upper duodenum[6]; therefore, the amount of pancreatic bicarbonate delivered upstream to the duodenal bulb may be decreased, resulting in a decreased pH in the duodenal bulb. In addition, patients with duodenal ulcer disease also have more rapid emptying of gastric contents; thus, the duodenal bulb is bathed for a longer time by acid.[7]

Major advances have been made in understanding the genetics of peptic ulcer disease. Until recently no clear pattern of heredity for duodenal ulcer disease has been identified. Data from a study by Rotter and colleagues,[8] however, suggest that in families with a high prevalence of duodenal ulcer, serum pepsinogen I levels are elevated, and that this abnormality is inherited as an autosomal dominant trait. It is now thought that this may account for as much as 50 percent of ordinary duodenal ulcer disease. If so, previous genetic theories of the pathogenesis of peptic ulcer, that is, so-called polygenic inheritance, may be incorrect. Polygenic inheritance implies that there are multiple genes involved in the expression of the clinical condition, and, therefore, a continuum of predisposition to the condition exists depending on the number of causative genes that a given person inherits. Genetic heterogeneity, on the other hand, implies that a particular disorder, such as duodenal ulcer disease, is really a group of disorders with different genetic and nongenetic causes. When these heterogeneous disorders are grouped, no clear mendelian pattern of inheritance can be discerned. It is only when a subclinical marker, such as serum pepsinogen I level, is followed that the mode of inheritance becomes apparent. Other conditions that may be examples of this concept include the mucopolysaccharidoses, the hyperlipidemias and diabetes mellitus. Other subclinical markers that can be studied to confirm the genetic heterogeneity of duodenal ulcer disease may be the serum gastrin response to ingestion of a meal or factors involved in gastric and duodenal motility. These remain to be elucidated; however, what has come of this concept is a new proposed classification of peptic ulcer disease (Table 1).[9]

Personality types of patients with ulcers have long been discussed. Alexander in 1934[10] described patients with ulcers as those with an excessive wish for dependency. In 1957, in a study of Army recruits, Weiner and co-workers[11] suggested that those in whom ulcers developed had an excessive wish to be loved, fed and cared for, which led to feelings of shame, anger and guilt, as these are infantile cravings contrary to expected adult standards. Weiner and his associates used these criteria along with the presence of an increased pepsinogen level in the blood to predict successfully the onset of peptic ulcer disease in Army recruits during basic training. Unfortunately, these studies have not been carried further since that time, and there are no convincing data now that any particular personality type is associated with peptic ulcer disease.

TABLE 1.—*Proposed Classification of Peptic Ulcer Disease*

Peptic ulcer associated with rare genetic syndromes (for example, multiple endocrine adenomatosis-I)
Gastric ulcer
Combined gastric and duodenal ulcer
Hyperpepsinogenemic I duodenal ulcer
Without postprandial hypergastrinemia
With postprandial hypergastrinemia
Normopepsinogenemic I duodenal ulcer
Without rapid gastric emptying
With rapid gastric emptying
Childhood duodenal ulcer
Duodenal ulcer associated with other chronic diseases

*Adapted from Rotter & Rimoin.[9]

A relationship between peptic ulcer disease and stress has been assumed for many years. William Beaumont noted that when he was observing Alexis St. Martin (a patient in whom a gastrocutaneous fistula had developed following a gunshot wound) during a period of emotional turmoil, he could demonstrate increased gastric secretions and definite changes in the gastric mucosa. Occupational stress and peptic ulcer disease have been studied as well. However, no increased incidence of peptic ulcer disease has been noted in business executives, in Massachusetts physicians in the 1960's or, recently, in air traffic controllers. It seems clear that air traffic controllers are a group under relatively high stress. Indeed, because of this assumption, the Federal Aviation Administration contracted a study to see what happened to the health of air traffic controllers over time. A group of 416 men, aged 25 to 46, were followed for three years; symptoms of ulcer disease developed in 13 of them. This would suggest an increased incidence of peptic ulcers. However, only three of these cases were documented as ulcers. The other ten

TABLE 2.—*Possible Forms of Therapy for Peptic Ulcer Disease*

Regulation of diet
Elimination of offending agents
Administration of antacids
Administration of antisecretory agents
Surgical intervention

patients had normal x-ray or endoscopic findings. Thus, the incidence of documented peptic ulcer disease in this population was 2.4 per 1,000 person-years versus an incidence in the general population of 2.1 per 1,000 person-years, not a major difference.[12] Finally, in a recent report by Thomas and colleagues,[13] no association was seen between incidence of chronic gastric ulcer and life stress events, as measured on various life-stress scales. Therefore, it is still difficult to be certain of the association of stress and personality types with peptic ulcers of the duodenum or stomach.

With this relatively broad overview of the pathogenesis of ulcer disease, what can we say about treatment? Treatment should follow from understanding the pathogenesis of the condition. Unfortunately, however, this is not always possible. We will discuss various aspects of treatment, including diet, elimination of offending agents, therapy with antacids or antisecretory agents and surgical treatment (Table 2).

There has been no evidence of the effectiveness of intensive milk and cream diets in the treatment of ulcer disease. In fact, there may be some potential harm as one retrospective study, done both here and in Great Britian, indicated that patients with ulcer who were treated with Sippy diets had a substantial increase in the presence of myocardial infarction at autopsy compared with those patients with ulcer disease who were not treated with a Sippy diet and those without ulcer disease.[14] This is a retrospective autopsy study, with all its attendant problems, but there certainly is no clear evidence that diets high in milk and cream have any benefit.

In the United States, bland diets have also been shown to be ineffective in at least five controlled trials since 1942. Welsh[15] surveyed 326 different hospitals in this country and found that, in spite of no evident benefit, the bland diet was the one most often prescribed for ulcer patients. In trying to define a bland diet, one finds a considerable variation in composition and nomenclature of the foods involved. There is absolutely no uniformity in what is defined as bland.

It is my recommendation that patients be kept on as normal a diet as possible, with the elimination of offending agents, which can take several different forms. Clearly, patients who report that certain foods offend their stomach should be advised to eliminate these from their diet. Cigarettes also are offending agents, to the stomach and duodenum, and patients with ulcer disease who are smokers should be strongly urged to discontinue smoking. Alcohol and coffee are known stimulants of gastric acid, and decaffeinated coffee is as strong a stimulus to gastric acid secretion as caffeinated coffee. However, because a meal is the greatest stimulus to gastric acid production, it would seem reasonable to allow judicious amounts of alcohol, such as a small glass of wine, with meals; however, this should certainly be avoided between meals. I believe that overall it is important for patients to maintain their normal life-style, if possible.

Antacids have been a mainstay of therapy for peptic ulcer disease since ancient times. Antacids must be palatable, as they do no good if they are left sitting on the bathroom self. Also, they must be given in effective doses and at the proper time. Antacids with a neutralizing capacity of 80 mEq of acid can maintain low gastric acidity for as long as four hours when administered one and three hours after meals.[16] Effective doses of antacids lead to more rapid healing of duodenal ulcers when compared with placebo therapy as shown in a study in which seven doses of 140 mEq of neutralizing capacity each were given per day (total 980 mEq per day). When many of us were in medical school we were told that antacids were good for pain but were not very good for healing ulcers. However, in the study cited above,[17] patients using antacids had no difference in their relief of pain compared with those using a placebo. This has been confirmed by a number of studies, both with long-term use and with single doses of antacids.[18] Therefore, the question that we often ask our patients, "Do you get pain relief when you take antacids," may be meaningless.

There is a great deal of variability in the neutralizing capacity of various antacids (Table 3). For example, in a study by Drake and Hollander,[19] Maalox Therapeutic Concentrate, was found to be most potent. However, 33 ml of this drug were required to neutralize 140 mEq of acid. This can be compared with Amphojel, of which 100 ml are required to neutralize 140 mEq of gastric acid. Further, 30 tablets of Digel or 70 tablets of Am-

phojel are required to neutralize the same amount of acid. Thus, if one really wants to get effective neutralization with these antacids, one has to chew an enormous number of tablets. In summary, it is important to understand that patients need to have effective doses of antacids to get effective treatment of peptic ulcer disease.

Antisecretory agents, particularly anticholinergic agents, have been used in treating ulcers for many years. They may still be useful because they possibly potentiate the H_2 antagonists; also, they may play an adjunctive role with antacids in treating patients with night pain. They are best tolerated when given as a nocturnal dose. However, the role of anticholinergic and other antisecretory agents is becoming less clear as more experience is obtained with alternative therapies.

The alternative therapy that is always discussed is cimetidine and other H_2 blockers. Based on about five years of clinical experience in this country and slightly longer in other countries, cimetidine therapy has been shown to be effective in healing duodenal ulcers.[20-21] It is clear also that cimetidine probably has few significant long-term adverse effects. A number of early reports suggested prompt recurrence of duodenal ulcer after cimetidine treatment stopped. However, studies of gastric acid secretion, both before and after treatment with cimetidine, have shown no significant change in either basal secretion or that after maximal stimulation. Although there have been transient increases in serum gastrin levels, there was prompt return of gastrin to basal levels (within several days) after cessation of therapy.[22] Various regimens have now been shown to be effective in decreasing the recurrence rate of ulcers once healing has occurred. However, even in the face of continuing treatment, recurrences are observed.

Several problems with cimetidine are worth noting. One has to adjust the dose in patients with impaired renal function, as the drug is excreted primarily by the kidneys (Figure 2).[23] There are also several side effects of this drug, of which we are becoming aware with increasing clinical experience.[24] A few cases of leukopenia have been described. Confusional states have been seen in elderly patients and in those with altered renal and hepatic function. There is apparently an antiandrogen effect, which may lead to gynecomastia and galactorrhea. Sexual dysfunction in males has been described, although the significance of this is not yet clear.

Practicing internists now face a difficult decision in choosing between antacids and cimetidine in the treatment of patients with duodenal ulcer. There is apparently no difference between effective antacids and cimetidine on the healing rate of duodenal ulcers.[25] One must give antacids orally or by way of a nasogastric tube, while cimetidine can be administered orally and intravenously. There is no sodium load with cimetidine, and there is a variable sodium load with various antacids. Cimetidine is now licensed for use for eight weeks of therapy during acute episodes and for indefinite periods in smaller doses as a prophy-

TABLE 3.—*Comparison of Various Antacids**

Antacid	*Acid Neutralizing Capacity: mEq/ml or tablet*	*Dose Containing 140 mEq (ml or tablet)*
Liquid Form		
Maalox Therapeutic Concentration	4.2	33 ml
Mylanta II	3.6	39 ml
Gelusel-II	3.0	47 ml
Maalox Plus	2.3	61 ml
Amphojel	1.4	100 ml
Tablet Form		
Camalox	16.7	8 tabs
Mylanta II	11.0	13 tabs
Tums	10.5	13 tabs
Titralac	9.5	15 tabs
Rolaids	6.9	20 tabs
Digel	4.7	30 tabs
Amphojel	2.0	100 tabs

*Adapted from Drake and Hollander.[19]

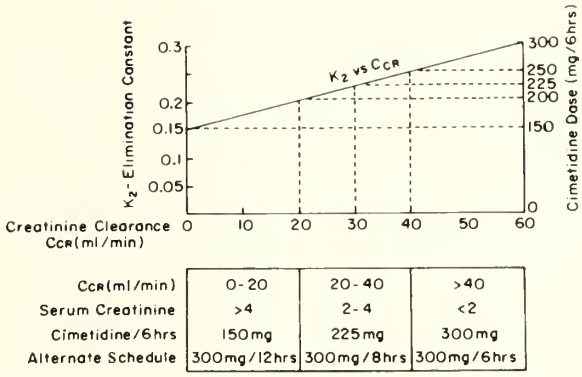

Figure 2.—Cimetidine dosage adjustment nomogram and table. A loading dose of 300 mg of cimetidine is first administered; the maintenance dose, given every six hours, is then determined by drawing a vertical line from the patient's creatinine clearance (Ccr) to meet the sloping line K_2 versus Ccr, and then drawing a horizontal line from the intercept to meet the dosage axis. To use the table, the adjusted maintenance dose is given in the column under the patient's Ccr (K_2 = elimination constant). (Reprinted with permission of Luk GD, Luk WJ, Hendrix TR: Ann Intern Med 90:991, 1979.)

laxis. There are no limitations on antacid use, although intensive treatment with antacids sometimes causes diarrhea, and in patients with renal failure the absorption of magnesium and possibly aluminum, may be substantial. A patient may be less willing to take large doses of antacids seven times a day than four tablets of cimetidine a day. Clearly, such lack of compliance is important. Finally, the cost of these compounds varies widely. I found recently that I could get 100 cimetidine tablets at my neighborhood discount drug store for $34.70, while the University of California, San Francisco (UCSF) pharmacy charges $24.00. There is also a highly variable cost of antacids. A survey of some pharmacies near UCSF and in other neighborhoods in San Francisco, showed that the cost of Maalox Therapeutic Concentrate, the most potent antacid examined in a recent study, ranged in price between $3.29 and $4.79 for a 12-oz bottle. If one takes two tablespoons of Maalox Therapeutic Concentrate seven times a day the drug cost of a 25-day program (comparable to 100 tablets of cimetidine) would range between $47.98 and $69.86. I think that we very rarely appreciate the costs to patients of our therapeutic regimens, both with respect to the financial expenses involved and the disruption of their lives in following our orders. Thus, it is important to determine appropriate therapy on the basis of each patient's ability to take these various drugs.

The final major question for internists with patients with ulcer disease is when is surgical intervention necessary? There are still four major indications for an operation: hemorrhage, perforation, obstruction and intractability. With respect to hemorrhage, two major bleeding episodes should be an indication for an operation. "Major" episodes are defined as those resulting in a hematocrit of less than 28 percent or requiring greater than 1,500 ml of volume replacement—usually whole blood—for resuscitation. The incidence of a second hemorrhage in a patient with duodenal ulcer is between 30 percent and 50 percent; this recurrence rate remains constant through multiple subsequent episodes. Therefore, it seems that two hemorrhages would be enough to indicate the need for an elective operation in these patients.

In several areas in the world perforation is treated medically with broad spectrum antibiotics and nasogastric suction. In this country, however, the presence of a perforated peptic ulcer is usually an indication for an immediate operation.

Obstruction of the gastric outlet due to an ulcer also can be an indication for surgical intervention, particularly if the obstruction is not relieved after 72 hours of medical therapy, including nasogastric suction and intensive treatment with antacids or H_2 blockers.

TABLE 4.—*Factors Responsible for Intractability in Peptic Ulcer Disease*

Intrinsic
Penetration of ulcer
Pyloric obstruction
Postbulbar ulcer
Channel ulcer
Hypersecretory drive states (such as gastrinoma)
Other chronic diseases
Extrinsic
Drugs
Smoking (?)
Caffeine (?)
Neuropsychiatric
Psychic stress
Inability to comply with medical regimen

Intractability of a peptic ulcer is most difficult to define and most difficult to treat. Intractability may be defined as either increasing frequency and severity of attacks of peptic ulcer disease or a poor response to medication with respect to relief of symptoms over a long course of treatment. Some patients cannot or will not assume responsibility for medical therapy, with its changes in life-style and difficulties in taking medications. The so-called intractable patient probably requires and deserves the same level of therapy as the intractable ulcer. When examining intractability, one must look at several factors to be sure that one is not dealing with a major complication or other cause of peptic ulcer disease. Factors that may be responsible for intractability (Table 4) include penetration of the ulcer, pyloric obstruction or unusual locations of the ulcer. One must also look for hypersecretory drive states, particularly the presence of hypergastrinemia and the Zollinger-Ellison syndrome, before subjecting a patient to an operation for peptic ulcer. The presence of other chronic diseases also can be associated with intractability. Extrinsic factors, such as drugs, smoking and caffeine, may also lead to intractability; these must be investigated and then eliminated as much as possible before carrying out an operation. It is clear from many studies that patients who are treated surgically because of intractability have the greatest incidence of postsurgical complications.

Several different surgical techniques have been developed to treat peptic ulcer,[26] including most

recently the highly selective or proximal gastric vagotomy in which the nerves to the gastric body and fundus are severed, leaving the motor neurons from the vagus to the gastric antrum intact. This operation has been associated with a much lower incidence of postsurgical complications, such as diarrhea and dumping; however, this procedure is associated with a fairly high recurrence rate of 5 percent to 10 percent.[27] The perfect surgical procedure—with no recurrence and no complications—has yet to be developed.

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Specialty Conference

Moderator

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Discussants

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Refer to: Guze PA, Bayer AS, Anthony BF, et al: Spectrum of human chlamydial infections—Teaching Conference, Harbor-UCLA Medical Center, Torrance (Specialty Conference). West J Med 135:208-225, Sep 1981

Spectrum of Human Chlamydial Infections

PHYLLIS A. GUZE, MD:* The genus *Chlamydia* is one of the most widespread groups of organisms found in nature and is responsible for a large number of human infections.[1-3] These pathogens are causative agents of ornithosis (psittacosis), inclusion conjunctivitis, neonatal pneumonitis, lymphogranuloma venereum (LGV), genital tract and other infections.[3-5] In this symposium, we will review the clinical manifestations of the diseases associated with chlamydiae. Table 1 lists the diseases and associated serotypes for the human chlamydial agents. I will begin by discussing the microbiology of these organisms.

Microbiology

In the genus *Chlamydia,* two species are recognized: *Chlamydia psittaci,* which causes ornithosis (psittacosis), and *Chlamydia trachomatis,* which is responsible for most human infections including LGV, trachoma. inclusion conjunctivitis, neonatal pneumonitis, epididymitis, urethritis, cervicitis, pelvic inflammatory disease and other related diseases. *C trachomatis* strains are human pathogens with man as the sole natural host, whereas *C psittaci* strains appear to involve human diseases only as zoonoses.

The chlamydiae are obligate intracellular parasites that multiply by binary fission. The organisms contain both DNA and RNA but are unable to sustain growth outside an animal cell. They are susceptible to many antibiotics.[6-8] These organisms, therefore, have characteristics of both viruses and bacteria.

Chlamydial agents depend on the host cell for energy and metabolites. The life cycle is approximately 48 hours and very complex. An extracellular elementary body attaches to a host cell (columnar epithelium), induces phagocytosis and is ingested. Within the cell it reorganizes into a larger initial body (reticulate particle) that divides by binary fission, producing daughter cells. Division ceases after 18 to 24 hours and the initial bodies condense to form elementary bodies that subsequently rupture out of the host cell and infect other cells.[1]

C trachomatis is distinguished from *C psittaci*

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ABBREVIATIONS USED IN TEXT

CF = complement-fixation
CNS = central nervous system
IC = inclusive conjunctivitis
LGV = lymphogranuloma venereum
micro-IF = microimmunofluorescent
NGU = nongonococcal urethritis
PGU = postgonococcal urethritis
PID = pelvic inflammatory disease
VD = venereal disease

by the formation, in the former, of compact, rigid-wall, intracytoplasmic inclusions that contain glycogen and are stained by iodine.[9] *C psittaci* inclusions are diffuse and are not stained by iodine. In addition, *C trachomatis* is much more sensitive to sulfonamides than is *C psittaci*.[4]

The chlamydiae that cause trachoma and inclusion conjunctivitis were first isolated by inoculation of clinical specimens into the yolk sac of embryonated hens' eggs.[10] This time-consuming method has precluded its use clinically. Gordon and Quan[11] introduced a tissue culture method for isolating these agents using radiated McCoy cells and employing centrifugation of the inoculum to facilitate cell infection. Modifications of this procedure are in use today as routine techniques for the isolation of these organisms.[12-17] The major methods for showing inclusions in the infected cells are by iodine or Giemsa staining or by immunofluorescence. It is important that adequate tissue samples are collected in all attempts to isolate *C trachomatis*. For example, in nongonococcal urethritis, endourethral specimens are preferred to discharge specimens; urine and urine sediments have not been suitable.[12,18]

All members of the genus share a common group complement-fixing antigen. The group complement-fixation (CF) tests for serum antibodies are useful in the diagnosis of LGV and psittacosis[19] but not in the diagnosis of trachoma, inclusion conjunctivitis or the genital tract infections.[20-21] A microimmunofluorescent (micro-IF) technique[22] that serotypes *Chlamydia trachomatis* is most useful in the diagnosis of oculogenital infections and trachoma. There are 3 serotypes of the LGV agent and 12 serotypes of the trachoma-inclusion conjunctivitis agents.[1] Table 1 lists the diseases most commonly associated with specific serotypes.

Wang and Grayston[22] initially introduced the micro-IF test in 1970 for serotyping the organisms, but further studies from the same and other laboratories found it also to be a highly sensitive and specific indicator of antichlamydial antibodies.[4,23-27] The micro-IF test is more sensitive than the complement-fixation test.[25] The presence of a reaction in a single serum specimen simply reflects previous exposure. A changing titer may be seen in patients examined early in the course of infection—however, patients are seldom seen at this time. Unfortunately, many of the infections caused by *C trachomatis* are chronic and, although the micro-IF test can detect IgG and IgM antibody (presumed early infection), there is evidence that the IgM response may last for approximately a month following infection.[27] The micro-IF antibodies (IgG) may persist for life, although in some patients they disappear spontaneously.[27] Microimmunofluorescence may also be used to test secretions for antibody activity. Thus, the demonstration of antichlamydial antibody in tears may support the diagnosis of trachoma.[28,29] This test will probably be applied in the future to genital tract secretions.

A fourfold or greater rise in titer in either the complement-fixation or micro-IF test will support the diagnosis of chlamydial infection in the clinical syndrome being considered. Unfortunately, this is usually not observed, and often the clinician must simply use a single titer that has to be interpreted

TABLE 1.—*Human Diseases and Associated Serotypes Caused by* Chlamydia*

Species	*Disease*	*Serotype*†
C psittaci	Ornithosis (psittacosis)	Many unidentified serotypes
C trachomatis ..	Lymphogranuloma venereum	L-1, L-2, L-3
C trachomatis ..	Trachoma (hyperendemic)	A, B, Ba, C
C trachomatis ..	Inclusion conjunctivitis (adult and newborn), pneumonitis, nongonococcal urethritis, epididymitis, cervicitis, salpingitis, peritonitis and perihepatitis, infective endocarditis, pharyngitis, otitis	D, E, F, G, H, I, J, K

*Modified from Schachter.[3]
†Predominant, but not exclusive, association of serotype with disease.

in terms of the patient's disease and the background prevalence of antibody titers.[1]

Study of any natural chlamydial host shows a substantial degree of latent or inapparent infections.[2,30] The LGV agent can persist in the human host for many years because sequelae sometimes occur years after infection.[31] Acute trachoma may develop in persons who have left trachoma-endemic areas and have not had active disease since childhood.[32] Inclusion conjunctivitis, generally considered a self-limiting infection, has been shown to persist in some persons.[4,33,34] It is doubtful that chlamydiae persist in the host in a nonreplicating form. It is more likely that latent or subclinical infections represent persistent low levels of multiplication held in check by host defense mechanisms.[3]

DR. GUZE: *We will now review the variety of diseases caused by these agents. Dr. Bayer will discuss ornithosis (psittacosis).*

Ornithosis (Psittacosis)

ARNOLD S. BAYER, MD*

"ORNITHOPULMONARY" DISEASES are a well-defined group of clinical pulmonary disorders resulting from exposure to birds, their feathers or their excreta. These include several infectious diseases, such as cryptococcosis, histoplasmosis, avian tuberculosis, and the entity for discussion in this section, ornithosis (psittacosis). An additional avian-associated disease is the immunologically mediated "pigeon-breeder's lung" (bird fancier's lung). A partial list of birds known to carry infective agents that cause pulmonary disease is shown in Table 2.[35]

For purposes of nomenclature, "ornithosis" is a general term referring to any avian-related infection cause by *Chlamydia psittaci;* "psittacosis" (parrot fever) refers specifically to such infections related to psittacine birds (such as parrots, cockatoos, parakeets and budgerigars). I will use the general term ornithosis throughout this discussion.

Epidemiology

Ornithosis is a true zoonosis contracted by exposure to infected birds. Most cases are traceable to exposure to exotic, imported avian species.

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TABLE 2.—*Ornithopulmonary Disease*

Disease	*Avian Genera Implicated*
Ornithosis (psittacosis)	Psittacine birds (parrots, cockatoos, parakeets) Nonpsittacine birds (pigeons, chickens, turkeys, ducks)
Cryptococcosis	Pigeons*
Histoplasmosis	Chicks, starlings, pigeons*
Avian tuberculosis	? Domestic birds and barnyard fowl

*Birds are not infected, but organism grows well in avian feces.

However, the disease is also recognized as a serious occupational hazard to people in the poultry trade, particularly in processing plants.[30,36] In such settings in the United States, turkeys are usually the type of bird implicated, while in Eastern Europe ducks have been the major source of industry-related ornithosis.[30] Also at risk for contracting ornithosis are pet shop personnel and people working in quarantine treatment centers for imported birds.

C psittaci causes natural infection of many avian species in the wild, but the chlamydial infection rate is relatively low.[37] However, as noted by Schachter,[3] there is an amplification of chlamydial infection that occurs by virtue of the crowding and stress involved in avian capture, shipping and quarantine. Therefore, newly imported birds represent a considerable health hazard to treatment center personnel and new bird owners. In the past, the United States depended on a system of chlortetracyline chemoprophylaxis given to birds in exporting countries before importation into the United States. This system was not satisfactory and has essentially been replaced by chlortetracycline prophylaxis administered to imported birds at US quarantine centers during their stay for Newcastle disease testing.[38] Unfortunately, there is no assurance that such preventive regimens are effective in eradicating *C psittaci* carriage. The failure of such an unsupervised program is evidenced by the recovery of the organism in avian excreta shortly after release from the US treatment centers.[39] In Germany, the unreliability of such a system has led to mandatory monitoring of chlortetracycline levels in birds given chemoprophylaxis before release from quarantine.[40]

It should be noted that *C psittaci* parasitizes the intestinal tract of lower mammals, as well as birds, and causes a variety of infectious syndromes in these animals including arthritis, pneumonitis,

TABLE 3.—*Differential Diagnosis of Ornithosis (Psittacosis)*

Mycoplasmal pneumonia
Q Fever
Legionellosis
Primary coccidioidomycosis
Primary histoplasmosis
Viral pneumonitis

abortion, enteritis, conjunctivitis and encephalomyelitis.[2] However, mammalian-associated *C psittaci* infection is not considered a serious threat to humans as these strains are of relatively low communicability or pathogenicity for man.[3] The most frequent human infection with such strains is conjunctivitis, related to exposure to cats with "feline pneumonitis."[41]

Although *C psittaci* infection may be fatal in birds, only minimal evidence of disease is usually apparent.[42] The chlamydiae are found in avian body fluids and can be transmitted to humans by inhalation of aerosolized infected particles. This may be infected droplets, droplet nuclei or dust. Of interest, human-to-human transmission has been described. Physicians, nurses and other medical personnel caring for patients with ornithosis may acquire the disease; therefore, respiratory isolation techniques should be followed when such patients require admittance to hospital. *C psittaci* pneumonitis contracted from turkeys, psittacine birds or from an ill patient appears to be more severe than disease acquired from other sources.[43]

Pathogenesis

After exposure to a large *C psittaci* inoculum, the human host experiences nasopharyngeal monocyte-macrophage parasitization. The subsequent spread of the agent to the lungs and other extrapharyngeal sites is probably by hematogenous dissemination.[42] This is unlike lower respiratory viral infections where progression of infection is often from pharynx to lung by way of aspiration and contiguous cell-to-cell spread.[44,45] Other organ systems involved in the initial hematogenous dissemination are liver, spleen, cardiac and skeletal muscle, and the central nervous system (CNS).[43] These foci are also sites of several important extrapulmonary *C psittaci* clinical syndromes.

Clinical Syndrome

Clinically and radiographically, ornithosis closely resembles other "atypical" pneumonias, including those due to mycoplasmas, Q fever, Legionnaires' disease, influenza, other viruses, primary coccidioidomycosis and primary histoplasmosis (Table 3).[44-48]

The incubation period is approximately 7 to 14 days but may be shorter in large-inoculum transmission, as in human-to-human spread. Although variable, the clinical illness is generally biphasic, with an initial constitutional syndrome and a later pneumonitis syndrome. The constitutional phase is featured by moderate to pronounced extrapulmonary complaints of fever, chills, headaches, myalgia, photophobia and sore throat.[43] The fever is initially low grade (less than 38.9°C [102°F]) but usually becomes high (39.4° to 40.6°C [103° to 105°F] during the latter part of the first week of illness. Headache, photophobia and nuchal myalgia are often so prominent as to suggest meningitis, and this usually results in a lumbar puncture to rule out that possibility. Additionally, delirium, agitation and disorientation have been particularly emphasized in certain epidemics of ornithosis, again suggesting a primary CNS disorder. Epistaxis is seen in about 25 percent of patients in the constitutional phase of the disease.[42] Patients may also have primarily gastrointestinal complaints during this phase, especially abdominal pain, distension, nausea and vomiting.

During the latter part of the first week, after the onset of fever, pneumonic symptoms become prominent. As in other atypical pneumonias, a dry, hacking, nonproductive cough is characteristically noted.[46,49] Hemoptysis may occur in severe cases, especially in patients with tussive paroxysms. Other symptoms commonly seen with classic bacterial pneumonitis, such as purulent sputum, chest pain and pleuritic complaints, are infrequently observed.[50] Most patients are not dyspneic; however, in those with severe multilobar involvement, symptoms of acute respiratory insufficiency may develop.[42] A clinical corollary is that associated *C psittaci* myopericarditis should be considered in patients with documented chlamydial pneumonitis presenting in respiratory distress but for whom evidence of extensive pneumonitis *is lacking* on x-ray studies of the chest.[51]

On physical examination, most patients have high fever and tachycardia. Most patients will have a "temperature-plus dissociation"[43,49] or "relative bradycardia" as is seen in enteric fever, brucellosis and legionellosis.[52,53] As in other atypical pneumonias, pulmonary auscultation

usually discloses fine crepitant rales without signs of true consolidation.[46] It should be mentioned that the radiographic evidence of pneumonitis is frequently much greater than would be predicted by physical examination.[42] Splenomegaly is often prominent (10 percent to 70 percent of cases),[42] in contrast to other atypical pneumonias, and is an important differential feature. Approximately 25 percent of patients will have a faint macular eruption (Horder's spots) occurring during the constitutional phase of illness. These lesions blanch with pressure, are evanescent and located mainly on the torso, thus resembling the rose spots of enteric fever.[54] Occasionally, tender hepatomegaly and jaundice may be seen and mimic viral hepatitis. This is an uncommon yet prognostically ominous finding. A striking feature of ornithosis may be diffuse muscle tenderness on palpation, mimicking leptospiral or trichinotic myositis.[55,56]

A rare but severe complication of this disease is infective endocarditis.[57,58] The psittacosis agent generally infects previously abnormal or damaged valves on the left side of the heart. Psittacosis endocarditis generally requires an ablative surgical procedure for cure.

Routine Laboratory Studies

Routine laboratory evaluation is usually not helpful in distinguishing ornithosis from other infectious pneumonias, especially the atypical pneumonia syndromes. The leukocyte count is generally normal, commonly with lymphocytosis.[42] Examination of cerebrospinal fluid usually shows no abnormalities. Of diagnostic importance, serum cold agglutinins are rarely present. In contrast, cold agglutinins are present in approximately 60 percent of patients with mycoplasmal pneumonia,[59] a close clinical mimic of ornithosis.

Findings on x-ray studies of the chest resemble most atypical pneumonias:[46] Infiltrates are usually patchy and rarely lobar; "phantom" infiltrates are frequent, in which radiographic lesions disappear from one lung segment, only to reappear in another segment or opposite lung, and pleural effusions are uncommon. On rare occasions, miliary or nodular lesions have been observed on the x-ray films.[42]

Diagnosis

Confirmation of the diagnosis requires either isolation of the organism or demonstration of a significant rise in antibody. *C psittaci* is present in the blood during the constitutional phase and in both blood and sputum during the pneumonic phase of illness. Moreover, *C psittaci* persists in bronchial secretions for weeks after the onset of disease.[42] The organism can be isolated by inoculation of appropriate specimens into mice or into chick embryo yolk sacs.[60] As these techniques are not routinely available, the diagnosis is usually confirmed serologically. *C psittaci* and the agent of lymphogranuloma venereum share the same group antigens that form the basis of the complement-fixation assay. Sera should be tested during the acute and convalescent phases of illness to detect either a fourfold rise or fall in antibody titer. CF antibodies in this disease are generally present after the second week of illness. Any single positive CF titer ($\geq$1:16) in a patient with a febrile illness compatible with ornithosis is presumptive evidence of the diagnosis.[43,60] As is true when serological findings are positive in other infectious diseases, prompt initiation of appropriate chemotherapy may blunt antibody rise for several weeks or months into convalescence.[42,43,60] False-positive CF assays have occurred rarely in patients with Q fever or brucellosis.[43]

Therapy

The tetracyclines are the drugs of choice because the organisms are uniformly tetracycline-sensitive. *C psittaci* organisms are variably sensitive to the penicillins, erythromycin and chloramphenicol. Therefore, these drugs remain second-line agents in treating this disorder.[42,43]

Ornithosis is usually a mild disease, with abatement of fever and respiratory complaints occurring gradually over ten days to two weeks without specific therapy. Clinical relapse is rare. Introduction of tetracycline treatment (2 grams per day given orally in adults) usually shortens the febrile period by several days to a week.

Alternatively, ornithosis acquired from psittacine birds or from human-to-human spread tends to be clinically severe, with sustained or remittent fever and persistent respiratory symptoms for many weeks. In this setting, tetracycline therapy generally causes rapid lysis of fever within the first five to seven days. In severely ill patients, intravenously administered tetracycline (10 to 15 mg per kg of body weight per day) may be substituted for oral therapy. It is recommended that tetracycline therapy be continued for at least seven days after defervescence to prevent clinical re-

lapse.[61] It should be emphasized that radiographic resolution may lag several days to weeks behind clinical recovery.

The prognosis in ornithosis is good, with complete recovery the rule. The major morbidity and mortality are seen in the rare cases of chlamydial hepatitis, perimyocarditis or endocarditis.

Chlamydial Infections in Young Infants

BASCOM F. ANTHONY, MD*

CHLAMYDIAL CONJUNCTIVITIS in newborn infants (inclusion conjunctivitis or inclusion blennorrhea) has been appreciated for years as a common disorder, and the relationship of this entity to sexually acquired infection of the maternal birth canal was recognized long before characterization of the responsible agent (*C trachomatis* of the "oculogenital" serotypes, D through K). Two recent findings are largely responsible for a revival of pediatric interest in these infections. One is that perinatal acquisition of chlamydiae involves multiple organ systems in addition to the eye, and the other is that infection of the respiratory tract results in a distinctive and rather common form of pneumonia in young infants.

Epidemiology and Incidence

It is clear that the oculogenital chlamydiae are important causes of conjunctivitis and pneumonia in young infants. Recently, the simultaneous appearance of results from three prospective studies (Table 4) provides an estimate of the actual incidence of these infections.[62-64] Pregnant patients were surveyed one or more times during pregnancy for cervical infection with *C trachomatis,* and infants born to infected and uninfected mothers were followed for six months to a year. Follow-up involved clinical observations, chlamydial cultures and serological testing. The maternal infection rate varied from 2 percent to 9 percent, possibly due to differences in the populations or in diagnostic methodology. The follow-up data on infants of infected mothers are in remarkable agreement. In 33 percent to 44 percent, chlamydial conjunctivitis developed, in 11 percent to 20 percent chlamydial pneumonia occurred and in 16 percent to 20 percent there were asymptomatic chlamydial infections. Overall, in 60 percent to 70 percent of infants exposed perinatally, clinical or subclinical infection developed. By contrast, conjunctivitis was rare and other chlamydial disease was nonexistent in control infants born to uninfected mothers.

Other recent data suggest that, in addition to overt or symptomatic infection of the eye and respiratory tract, rectal and vaginal infection of newborns may be common.[62,65] It has also been suggested that chlamydiae acquired perinatally may play a role in serous and recurrent otitis media in young infants.[3,64]

Neonatal Conjunctivitis

Oculogenital chlamydiae are the most common specific cause of purulent conjunctivitis in newborns, but it is difficult to distinguish this clinically from other forms of neonatal ophthalmia. The symptoms usually begin at between 5 and 14 days of life but can appear earlier or later. Initial involvement is usually unilateral. In addition to a

TABLE 4.—*Prospective Studies of* Chlamydia *in Pregnancy and Infancy*

	Locale of Study		
	Denver[62]	*Boston*[63]	*San Francisco*[64]
Total number of women	340	322	900
No. positive (percent)	30(9)	6(2)	36(4)
Cultures/patient	2.3	1	1
Infants of positive mothers	18	6	20
Conjunctivitis (percent)	8(44)	2(33)	7(35)
Pneumonia (percent)	2(11)	1(17)	4(20)
Subclinical infection (percent)	3(16)	1(17)	4(20)
Total infected (percent)*	11(60)	4(67)	14(70)
Infants of negative mothers	16	89	18
Conjunctivitis (percent)	1(6)	3(3)	0

*Some infants had both pneumonia and conjunctivitis.

TABLE 5.—*Clinical and Laboratory Features of Chlamydial Pneumonia in Infants*

Onset	2 weeks to 2 months of age, usually insidious
Symptoms	Cough ("staccato"), tachypnea, nasal obstruction; usually mild
Physical findings	Afebrile rales, expiratory wheezes
Chest radiograph	Hyperexpansion, interstitial infiltrates
Laboratory findings	Eosinophilia, hyperimmunoglobulinemia

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purulent yellow discharge there are varying degrees of palpebral and bulbar inflammation and edema. Symptoms may persist or recur for weeks or months. Sequelae resembling those of trachoma are rare, but subtle changes (micropannus and conjunctival scars) apparent months or years later are relatively common.[62,66]

Chlamydial Pneumonia

The features of chlamydial pneumonia,[67-69] a fairly characteristic syndrome, are summarized in Table 5. The usual symptoms are tachypnea, staccato cough and nasal obstruction, beginning insidiously between two weeks and two months of age. Some infants have been symptomatic almost from birth and in a few, symptoms have developed in the third through fifth months of life. Fever is rare, the illness is generally mild, and many infants continue to thrive and grow normally. However, severe respiratory distress and apnea have been documented. Approximately half of the infants with this syndrome will have had conjunctivitis.[67]

When a physician is consulted (often after several weeks of low-grade illness), conjunctivitis may or may not be present. On examination, inspiratory rales are common and expiratory wheezes are variable. X-ray films of the chest show generalized hyperinflation of the lungs, scattered interstitial infiltrates and even areas of consolidation.

Certain readily available laboratory studies provide evidence that supports the diagnosis of chlamydial pneumonia. Eosinophilia is common, with absolute counts of 300 to 400 per cu mm or greater. Serum immunoglobulin levels are elevated, often to adult levels or higher. IgM and IgG are most consistently increased and IgA is often elevated.

Diagnosis

Specific diagnostic procedures are not yet widely available and usually require special arrangements. The definitive diagnosis of chlamydial infection in infancy is best made by isolation of the organism. If this is undertaken, direct scrapings or swabs of the conjunctival surface (rather than obtaining the exudate) or throat, or collections of nasotracheal secretions should be preserved in special medium pending transportation to a laboratory with the capability for chlamydial isolation.

Infants with conjunctivitis and pneumonia commonly demonstrate elevated antibody titers by micro-IF, but the serological diagnosis is complicated by passively acquired maternal antibody. Therefore, serial titers or testing for specific IgM antibody may be helpful. Showing chlamydial inclusions in conjunctival cells with Giemsa stain is a relatively sensitive and specific method for diagnosing chlamydial ophthalmia[3] and is widely available in clinical laboratories.

If specific diagnostic studies are unavailable or pending, it may be reasonable to institute antimicrobial therapy for a symptomatic infant whose illness is compatible with chlamydial pneumonia by clinical and laboratory criteria (eosinophilia and hyperimmunoglobulinemia).

Treatment

Neonatal chlamydial conjunctivitis is usually treated with topical tetracycline, sulfacetamide or erythromycin. Because of documented relapses and treatment failures with topical therapy,[70] and because of the likelihood that the conjunctival sac is only one of several body sites harboring *C trachomatis*,[65] two or three weeks of systemic therapy (erythromycin or sulfisoxazole) has been proposed.[70,71]

In an uncontrolled study of chlamydial pneumonia in infants, two weeks of systemic therapy with erythromycin (40 mg per kg of body weight per day) or sulfisoxazole (150 mg per kg of body weight per day) was associated with apparent eradication of chlamydiae from the respiratory tract and clinical improvement.[72]

Unresolved Questions

Recent new data on chlamydial disease have obviously expanded the role of these agents in certain common diseases of infancy. They have also raised questions about established procedures in the care of newborn infants. Because silver nitrate prophylaxis for gonococcal ophthalmia is apparently ineffective against chlamydiae, critics of Credé's regimen have an additional argument for an alternative, less irritating prophylaxis (topical tetracycline or erythromycin), which might prevent both infections. It should be pointed out that no regimen has been rigorously evaluated for the prevention of either chlamydial or gonococcal infection.

Although topical antimicrobial drugs are widely used for treating chlamydial conjunctivitis in newborns, this approach warrants reassessment vis-a-

vis systemic therapy (erythromycin or sulfisoxazole) in view of reported treatment failures with topical therapy and the probable desirability of clearing chlamydiae from other body sites in these infants.

The documentation of chlamydial disease in a young infant almost certainly indicates infection in the mother. Under these circumstances, it may be appropriate to recommend a therapeutic course of tetracycline in both parents.

DR. GUZE: C trachomatis *is the causative agent for lymphogranuloma venereum (serotypes L1-3) and other genital diseases (serotypes D through K). Dr. Tillman will discuss lymphogranuloma venereum, and I will then review the other male and female genital infections.*

Lymphogranuloma Venereum

DAVID B. TILLMAN, MD*

LYMPHOGRANULOMA VENEREUM (LGV) is a venereal disease (VD) caused by *C trachomatis*. It has also been called Durand-Nicolas-Favre disease, tropical bubo and lymphogranuloma inguinale. The infection involves primarily the lymphatics and lymph nodes of the genital area. Acute inguinal lymphadenitis is the most common manifestation. Late complications include strictures (rectal and urethral) and genital lymphedema. Although the disease was first described about 150 years ago, the causative agent was not isolated until 1940. Strains of *C trachomatis* isolated from patients with LGV show some biological differences from other strains of the organism. Of greatest clinical importance is an increased invasiveness and an affinity for lymphoid tissue rather than epithelial cells.[73]

Epidemiology

Although cases of LGV are found in most areas of the world, the greatest number occur in the tropical and subtropical areas of Africa and Asia. In the United States, LGV is endemic at a low rate and is seen primarily in the Southeast in blacks of low socioeconomic status. The disease is usually transmitted by sexual contact, but nonvenereal transmission has been reported following direct contact with infected tissues and fomites.[74] The frequency of transmission following sexual contact is not known. For unknown reasons, clinical infection is more common in males than in females.

Clinical Manifestations

A primary genital lesion occurs from three days to three weeks after exposure. It is a small, painless vesicle or ulcer located on either the penis or on the labia or vagina. It is noticed by less than a third of men and by even fewer women. It heals within a few days and is usually diagnosed retrospectively only when lymphadenitis appears.

From the site of primary infection the organism spreads by way of the lymphatics, and painful inguinal and femoral adenopathy occurs. The adenopathy is usually unilateral but can be bilateral. Progressive periadenitis leads to a matted mass of nodes that become fluctuant and suppurative. Enlargement of nodes above and below the inguinal ligament leads to the characteristic "groove sign," but this occurs in only a third of the cases.[75] Spontaneous healing eventually occurs. Constitutional symptoms such as fever, chills, headache, myalgias and arthralgias are common when regional adenopathy is present.

Primary anorectal infection occurs in women and homosexual men following anal intercourse. The organism infects intestinal epithelial cells and causes symptoms such as bloody or mucopurulent rectal discharge, tenesmus or diarrhea.

Early complications of LGV infection include bacterial superinfection, perirectal abscess and fistula formation. Late complications include rectal or urethral stricture and, uncommonly, elephantiasis of the penis or vulva.

Diagnosis

Although LGV is an uncommon disease, it is in the differential diagnosis of many common conditions such as inguinal lymphadenopathy, ulcerative genital lesions, perirectal abscess and fistula. At present, there are no entirely satisfactory ways to confirm or rule out the diagnosis of LGV. The best method is isolation of an LGV strain of *Chlamydia*. However, this method is positive only 30 percent to 50 percent of the time.[74] A complement-fixation test is available and is positive ($\geq$1:16) in 80 percent of cases. Unfortunately, it is not specific for acute infection because a

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rising titer is often difficult to demonstrate.[75] An intradermal skin test is commercially available, but it is not sensitive and is not currently used.[76] Micro-IF and counter immunoelectrophoresis tests have also been described. Both seem more sensitive and specific than older methods of diagnosis.[27,77]

Treatment

Treatment should consist of tetracycline, 500 mg taken four times a day for three to four weeks, or a sulfanamide, 1 gram taken four times a day for three to four weeks. Although this therapy will not cause early disappearance of a bubo, constitutional symptoms often disappear quickly. It is uncertain whether antibiotic therapy prevents late sequelae such as rectal strictures.

Male Genital Infections

PHYLLIS A. GUZE, MD

Chlamydia trachomatis IS A major cause of nongonococcal urethritis (NGU), postgonococcal urethritis (PGU) and epididymitis. Postgonococcal urethritis will be discussed with NGU.

Nongonococcal Urethritis

Nongonococcal urethritis is an extremely common sexually transmitted disease. In Great Britain, NGU is now at least three times as common as gonorrhea in men.[78,79] Although national statistics are not available in the United States, NGU is seen at least twice as often as gonorrhea in many venereal disease clinics[79,80] and private physicians' offices.[81] It is up to ten times more frequent than gonorrhea among men attending university health services.[81,82] Overall, it appears that NGU is at least two to three times as common as gonorrhea. Whereas gonorrhea is more common in homosexual males, blacks and persons of lower socioeconomic status, the frequency of chlamydial urethritis is higher than gonorrhea in whites, heterosexuals and persons of higher socioeconomic status.[83]

Evidence that 30 percent to 50 percent of cases of NGU are caused by *C trachomatis* has been substantiated by many groups.[84] Studies have repeatedly shown that *C trachomatis* can be isolated from the urethras of 30 percent to 50 percent of men who have NGU,[80,83,85-90] 20 percent to 30 percent of men with urethral gonorrhea,[80,83,85,91,92] and only 0 percent to 7 percent of men without urethritis.[80,83,85,87,88] Postgonococcal urethritis develops in 5 percent to 38 percent of patients with chlamydial-negative gonococcal urethritis, whereas this complication develops in approximately 80 percent to 100 percent of men with chlamydial-positive gonococcal urethritis (double infection).[85,89,92-94]

Clinical Manifestations

Generally, symptoms may be consistent with gonococcal urethritis: dysuria, urethral discharge or urinary frequency. Urinary frequency is rarely the only symptom.[95] NGU usually begins insidiously with a scant, watery discharge, although some patients have no discharge at the time of examination. The discharge is typically clear or white in color, thin and mucoid in consistency, and scant. Often it is demonstrable only after penile stripping.[96] In others, a copious purulent discharge is present. As many as 29 percent of patients with NGU are conscious of the discharge only in the early morning.[97] Female sexual partners of these men may give a history of acute or recurrent cystitis.[95] Prostatic enlargement and tenderness may be present.[98]

Diagnosis

The presence of urethritis should be confirmed by demonstrating an abnormal number of polymorphonuclear cells in the discharge[99,100] or in a first voided urine specimen.[83] Gonorrhea must be ruled out on the basis of Gram stain and culture. The identification of Gram-negative diplococci within polymorphonuclear cells correlates with the culture-positive diagnosis of gonorrhea in 98 percent of the cases, and failure to find the typical gonococcal organisms correlates with the diagnosis of NGU.[101] Establishing the cause of NGU as due to *C trachomatis* requires either cytologic diagnosis, chlamydial isolation or serodiagnosis.[1,102] Unfortunately, these tests are not routinely available.

Treatment

Patients with NGU should be treated with tetracycline, 250 to 500 mg four times a day for 7 to 21 days.[84,103-105] The exact length of time has not been established, although seven days is probably sufficient.[84,103] The dosage of 500 mg tetracycline four times a day for five days will also eradicate

Neisseria gonorrhoeae.[106] If tetracycline is contraindicated, erythromycin or sulfisoxazole for 14 days can be given.[5] The patient's sexual partners should also be treated.

If signs of urethritis persist, patient compliance must be considered, along with the possibility that not all sexual partners have been properly treated. About 70 percent of the female sexual partners of male patients with chlamydial urethritis have chlamydial infection of the cervix, and delay in treating these persons may lead to reinfection.[1,3,107] Additionally, other causes of NGU, such as *Trichomonas,* should be sought.

Epididymitis

A major role for *C trachomatis* in causing epididymitis was strongly suggested by the isolation of the agent from the epididymal aspirates of five of six men younger than 35 with "idiopathic epididymitis."[108] In this study, coliform organisms were responsible for epididymitis in the men 35 years of age and older. A prior study showed a significant rise in titer of chlamydial antibodies in two patients with acute epididymitis, which also suggested that *Chlamydia* is a cause of this disease.[109] Treatment is the same as recommended for NGU.

Female Genital Infections

PHYLLIS A. GUZE, MD

C trachomatis HAS BEEN isolated primarily from the cervix,[1,3,4,80,110-112] although organisms have also been recovered from the urethra,[12,86,113,114] upper genital tract[115,116] and peritoneal cavity.[117] I will arbitrarily divide the discussion of female genital tract infections into lower tract disease (cervix and urethra) and upper tract disease (salpingitis, pelvic inflammatory disease and peritonitis).

Lower Tract Infections

Cervicitis

Isolation of *Chlamydia trachomatis* from the cervix was first reported by Jones and co-workers in 1959.[118] Since that time a number of investigators have demonstrated chlamydial cervical isolation. Workers in this area have reported higher recovery of chlamydiae from women with cervicitis than from women with no abnormal findings.[110-112,119,120] The agent has been recovered from selected women with hypertrophic cervical erosions, mucopurulent endocervical discharges (mucopurulent cervicitis) and other cervical abnormalities.[111] However, approximately 5 percent of unselected women may be culture-positive without symptoms or cervical abnormalities.[121] So it appears that cervical infection with chlamydiae may range from asymptomatic disease through a spectrum of cervical abnormalities.

The symptoms observed in women with chlamydial infection are not distinctive and many women are asymptomatic. A structurally normal cervix is unlikely to be colonized by *C trachomatis.* However, the presence of higher grades of cervical discontinuity,* with or without purulent secretion, may indicate chlamydial infection, particularly if *N gonorrhoeae* and *T vaginalis* have been excluded as pathogens.[110]

The isolation of chlamydiae from normal cervices of asymptomatic women does not imply that these organisms do not act as pathogens. Indeed, the presence of these intracellular parasites means infection, at least at the cellular level. There is evidence that cervical infection can persist for many months,[112] and it is known that contacts of men with NGU have a higher incidence of chlamydial isolation.[80,111] It appears that chlamydial cervical infection may contribute to the high incidence of chlamydial NGU and is the basis for infection of neonates.

Diagnosis

Unfortunately, there are no specific signs or symptoms that specify *C trachomatis* infection. Several investigators have described a distinctive hypertrophic cervicitis with follicles that they feel are macroscopically characteristic of cervical chlamydial infection.[111,122,123] However, the validity of this finding is in question.[113] A history of NGU in the patient's partner is suggestive. There is a significant relationship between the presence of chlamydial antibodies in genital secretions and the isolation of chlamydiae,[124] but neither of these laboratory tests is readily available.

Treatment

The treatment schedules recommended for men with NGU are also applicable to women with

*Cervical discontinuity is a demarcated area usually spreading outwards from the external os, whose appearance differs from that of normal cervical epithelium.[110]

genital chlamydial disease. However, a 21-day course seems to be necessary for resolution of cervical abnormalities.[111]

Urethritis

A study of women contacts of men with NGU showed that 25 percent of the women excreted *C trachomatis* from the urethra only.[113] Urethral symptoms (burning, dysuria and frequency) were complained of much more often by those excreting *C trachomatis* from the urethra than by those excreting the agent from the cervix alone. A more recent prospective study implicated *C trachomatis* infection in 10 of 16 patients with the urethral syndrome who had sterile bladder urine and pyuria.[125] These studies suggest that *C trachomatis* may be a significant cause of abacterial urethritis in sexually active young women. Clarification of this issue awaits further studies.

Upper Tract Infections

Salpingitis and Pelvic Inflammatory Disease

The role of chlamydiae in diseases of the female genital tract, other than cervicitis, is just being elucidated. Eschenbach and co-workers[126] showed seroconversion in 15 of 74 women with pelvic inflammatory disease (PID) but recovered chlamydiae from the peritoneal fluid in only one patient. Mårdh and his colleagues[115] found that 30 percent of women with PID that they studied had chlamydial infection of the fallopian tubes as sampled at laparoscopy. A report by Paavonen and associates[116] showed that 26 percent of their study group with acute salpingitis were culture-positive for *C trachomatis,* and 43 percent of 72 patients from whom paired sera were obtained had either positive culture results for or seroconversion in the immunofluorescent test to *C trachomatis.* This seroconversion has also been documented in other work.[126,127] In the past, it was observed that in a series of mothers of infants with inclusion blennorrhea there would be some cases of PID. Currently, it is difficult to completely assess the role of chlamydiae conclusively in this disease, but it is likely that these organisms account for a proportion of cases of nongonococcal PID.

Diagnosis depends on culture isolation of *C trachomatis* from the fallopian tubes or cul-de-sac aspirate. Treatment has not been evaluated, but tetracycline has been recommended.[5]

Peritonitis

A possible role for *C trachomatis* in causing peritonitis and perihepatitis has been suggested by recent reports.[117,128] Muller-Schoop and co-workers[117] presented serological evidence of recent *C trachomatis* infection in 9 of 11 women who had acute peritonitis. Five of these patients had no evidence of gonococcal infection. Wolner-Hanssen and colleagues[128] reported four patients with peritonitis and perihepatitis, diagnosed by laparoscopy, who had positive cervical cultures only for *Chlamydia.* Chlamydiae seem to be plausible candidates for patients with nongonococcal Fitz-Hugh-Curtis syndrome.[117]

DR. GUZE: *Dr. Richard Bills will now discuss adult inclusion conjunctivitis and trachoma. I will finish this symposium with mention of some of the miscellaneous infections caused by chlamydiae.*

Adult Inclusion Conjunctivitis

RICHARD BILLS, MD*

ADULT INCLUSION CONJUNCTIVITIS (IC) is a follicular inflammation of the conjunctiva resulting from inoculation of the eye with genital secretions contaminated with chlamydiae. The infection clinically resembles the early inflammatory stages of trachoma but is associated with those strains of *C trachomatis* that cause genital infection (serotypes D through K) rather than the typical trachoma strains (serotypes A, B, Ba and C). Adult IC is primarily a disease of sexually active adults, the peak incidence occurring in the second and third decades.[129] The disease is almost always venereally transmitted either by direct oral-genital sexual activity or passive transfer of genital secretions to the eye. Reports of epidemics associated with potentially contaminated swimming pools do not rule out the possibility of venereal transmission and have been questioned.[1,130] Conjunctivitis is usually accompanied by concurrent genital infection (cervicitis, urethritis) in the patient or a sexual partner.[88,129] Unlike trachoma, eye-to-eye transmission is thought to be infrequent but accounts for reports of IC in elderly persons exposed to neonatal chlamydial conjunctivitis.[131] Although the disease has a worldwide distribution and vari-

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ations in geographic prevalence are suspected, documentation is unavailable. There does not appear to be an increased incidence in male homosexuals.[1]

Clinical Presentation

Experimental infection in human volunteers has shown an incubation period of 3 to 19 days.[132] Onset is acute with symptoms of tearing, burning, photophobia, a foreign body sensation and a slight mucopurulent discharge. Seventy percent of cases are unilateral. Ipsilateral, nontender, preauricular lymphadenopathy may be present. Examination at this stage shows hyperemia, papillary hypertrophy, superficial punctate keratitis with subepithelial corneal infiltrations and swelling of the limbal border. Typically, the inflammation is more severe on the inferior conjunctiva, but the entire mucosal surface may be affected. Serous otitis media occurs in a minority of patients and is usually asymptomatic.[133] Transient hearing loss has been reported.[134] Culture of middle ear aspirates for *Chlamydia* may be positive.[88] Follicular pharyngitis and anterior uveitis are uncommon findings.[1,135] Symptoms reach a peak by the third week, at which time ptosis and conjunctival lymphoid follicles are frequently seen. Without treatment the disease is generally self-limited with resolution over 3 to 12 months. Occasional patients demonstrate a less benign course. Inflammation continues and extensive corneal involvement results in scarring and neovascularization (pannus formation), with rare cases of visual impairment.[129,135] Severe IC is clinically indistinguishable from the later stages of endemic trachoma.

Diagnosis

A tentative diagnosis of adult inclusion conjunctivitis can be made clinically, but laboratory confirmation of *Chlamydia* as the cause is required. Definitive diagnosis is made by demonstrating the agent by morphology in tissue or growth in culture; serological testing is of limited diagnostic value.

A variety of laboratory techniques are available. Giemsa staining of conjunctival scrapings obtained during the acute phase shows a predominance of neutrophils with a scattered number of mononuclear cells. The diagnostic intracytoplasmic inclusions are scarce, and an experienced microscopist is needed for their correct recognition.[136] Scrapings have been positive in up to 60 percent of suspected cases when examined by experienced personnel.[88] Fluorescent antibody staining provides an even higher yield (80 percent) but is less specific.[137] Unlike endemic trachoma, there is rarely concurrent bacterial infection.[129] Growth of chlamydiae in tissue culture is possible using a variety of cell lines. Isolation is positive in 60 percent to 80 percent of suspected cases.[24,138] There is rough correlation between the degree of active inflammation and the ease of isolation of the organism in culture.[24]

Assays for antibody to chlamydial group antigen by complement-fixation are positive in 50 percent to 75 percent of culture-positive adults with conjunctivitis.[24,139] Type-specific serum antichlamydial antibodies (IgG and IgM) are detectable by micro-IF techniques in virtually 100 percent of patients,[138,140] but they are also positive in 24 percent to 40 percent of unaffected normal adults and 60 percent of patients in a metropolitan VD clinic.[129] Rising titers are found only occasionally with adult IC as genital infection usually precedes ocular involvement, and the serological response has already stabilized when the conjunctivitis develops. In general, serological testing has limited usefulness. Identification of antichlamydial antibodies (IgG and IgA) in tear specimens is more specific for ocular infection but is not widely available.[29,102,141]

Differential Diagnosis

Inclusion conjunctivitis must be distinguished from other forms of acute follicular conjunctivitis. The major differential entities are adenoviral conjunctivitis and herpes simplex keratoconjunctivitis. Differentiation is usually apparent by the shorter course of viral conjunctivitis (one to three weeks), the predominance of mononuclear cells in conjunctival scrapings and the findings on slit-lamp examination (for example, dendritic corneal ulcer). Viral isolation is the definitive diagnosis.

Treatment

The treatment of choice for adult IC is systemic tetracycline (1 to 2 grams per day for three weeks) or erythromycin (1 gram per day for three weeks).[139,142] Response is prompt with resolution of symptoms within 48 hours. Several months may be required for resolution of lymphoid follicles and corneal opacities.[1,137] Cultures become negative within 24 hours of initiation of therapy. Cytologic findings from scrapings may remain positive for several days.[138]

Topical antibiotics may diminish symptoms but

do not eradicate the organism.[139] Topical steroids prolong the course and have been associated with worsened inflammation on discontinuation.[139] Neither is recommended. Resistant infections are usually the result of reinfection rather than resistant organisms or relapse. It is essential to treat all sexual contacts with the same antibiotic regimen if reinfection is to be prevented.

Trachoma

RICHARD BILLS, MD

TRACHOMA IS A chronic inflammatory disease of the conjunctiva and cornea, which continues to be the most common cause of preventable blindness in the world today.[137] The disease was widespread in the Mediterranean basin in antiquity and became epidemic in Europe following the return of the French troops from the Egyptian campaigns under Napoleon. Improved sanitation and standards of living during the past 100 years have essentially eliminated trachoma in developed countries. It remains endemic in northern Africa, the Middle East, India and Southeast Asia. In North America, small endemic pockets of trachoma are still present among southwestern Native Americans.[32,143]

Pathogenesis

Endemic trachoma results from conjunctival infection with serotypes A, B, Ba and C of *C trachomatis*. Total Ba is most frequently isolated from Native Americans.[4] The organism is transmitted from person to person by direct contact with infected conjunctival secretions.[144] Hands, contaminated clothing and towels, and flies or gnats which feed on the eye discharge are felt to serve as important vectors.[135] Transmission is facilitated by conditions associated with poor sanitation, unavailable household water supply and environmental crowding.[130]

Intensive studies of endemic trachoma in Tunisia[144,145] and Taiwan[146] have shown that infection is acquired early in life and active disease is most prevalent in children younger than 10 years old. In certain communities virtually all children are infected by 2 years of age. The prevalence begins to decline by 5 years of age and reaches a stable rate of less than 5 percent of active inflammatory disease in adults.[144] However, conjunctival scarring continues into adulthood even as active inflammation wanes with adolescence.

Clinical Presentation

Symptoms of the initial infection may include a burning or foreign body sensation and a moderate mucoid discharge without systemic symptoms. Examination shows a nonspecific follicular conjunctivitis principally affecting the upper tarsal plate. There is a mixed neutrophilic and mononuclear infiltrate of the conjunctiva and variable papillary hypertrophy. Aggregates of lymphocytes with germinal centers known as conjunctival follicles appear as grey-yellow avascular elevations measuring 0.2 to 2 mm in diameter. If there is no recurrence of the infection, the evolution of the disease resembles that of adult inclusion conjunctivitis, with seroconversion and complete healing over the course of a year without specific therapy.[146] Reinfection is inevitable in endemic areas, however, and most children have continued active inflammation.[137]

As the disease progresses, scarring of the conjunctiva occurs. Initially, there may be only fine linear scars on the upper tarsal plates, while confluent areas of fibrosis are found in severe cases. Several authors[137,147] have suggested that conjunctival follicles and progressive scarring result from the host's hypersensitivity to chronic chlamydial antigenic stimulation during reinfection.

Involvement of the bulbar conjunctiva characteristically begins at the superior margin of the globe, with subepithelial inflammatory infiltrates (punctate keratitis) progressing to fibrosis and neovascularization of the mucosal surface. The resulting fibrovascular membrane (pannus) extends to the limbus and eventually involves the cornea itself.[139] There is swelling of the limbal border with circumferential lymphoid follicles. Regression of these follicles with scarring results in small depressions surrounding the cornea (Herbert's pits) that are pathognomonic. Corneal involvement typically begins at the superior border, but eventually all meridians are involved. Rarely is the pannus extensive enough to cover the pupil or obscure vision.[137]

Blindness occurs in adults and results from the sequelae of lid distortion combined with secondary bacterial infection.[135] Progressive conjunctival scarring during adulthood causes distortion of the tarsal plates with inward turning of the eyelids (entropion) and the eyelashes (trichiasis). The misdirected eyelashes constantly abrade

the corneal surface, resulting in superficial ulcerations that frequently become superinfected by bacteria. *Hemophilus* sp and *Moraxella* sp are the most common ocular bacterial pathogens in trachoma-endemic areas, occurring as epidemics of purulent conjunctivitis in the spring and summer.[145]

The combination of repeated corneal trauma, progressive scarring of the mucosal surfaces and superimposed bacterial infections contribute to the visual loss.[135] The damage is further exacerbated by fibrosis and occlusion of the lacrimal duct, with development of the "dry eye syndrome."[137] Blindness is extremely rare before the age of 30, even in hyperendemic areas.[144] Continued scarring of the conjunctiva and cornea can be seen as long as 20 to 40 years after cessation of active inflammation at a time when the chlamydial pathogens are no longer demonstrable by laboratory means.[142]

Diagnosis

In 1962 the World Health Organization published criteria for the diagnosis of trachoma.[148] Diagnosis can be made if two of the following clinical features are present: lymphoid follicles on the upper tarsal plate, typical conjunctival scarring, vascular pannus or limbal follicles or their sequelae, Herbert's pits. While such guidelines are useful for epidemiological surveys in endemic areas, they do not address the early stages of active inflammation. Laboratory confirmation of the clinical diagnosis is required during early stages to differentiate trachoma from other forms of chronic follicular conjunctivitis. This is accomplished by morphological identification of the organism in tissue, by culture or by rising serological titers.[149] The various techniques are discussed in the section on adult inclusion conjunctivitis. Endemic trachoma, however, presents unique diagnostic features. Conjunctival scrapings are positive for typical inclusions in less than 10 percent of adult patients by Giemsa staining and in 20 percent to 50 percent by fluorescent antibody staining.[21,150] Studies have shown that the ease of demonstration of the organism in scrapings has a rough correlation with the degree of active inflammation[21,102] and the endemicity of trachoma within the community.[24] Scrapings have a low yield in adults with little active inflammation and in the scattered areas of endemicity in North America.

Complement-fixation titers for chlamydial group antigens are positive ($\geq 1:16$) in approximately 20 percent of affected patients,[21] while micro-IF titers are positive ($>1:8$) in up to 70 percent.[24] It must be emphasized that these serological results only document prior exposure and do not provide definitive evidence of current infection.

Although culturing of the organism is possible from trachoma patients, it is of little practical use in most rural endemic areas.[136] Culture techniques have been employed in studies of Native Americans, but the yield has been low.[143] In general, diagnosis in endemic areas has relied on Giemsa staining or, more recently, fluorescent antibody staining of scrapings combined with typical clinical findings.

Differential Diagnosis

The clinical diagnosis of trachoma in the later stages is seldom difficult. Early disease, however, presents as a nonspecific follicular conjunctivitis. The differential diagnosis includes toxic follicular conjunctivitis resulting from chronic exposure of the eye to foreign substances (such as cosmetics or medications), allergic keratoconjunctivitis, bacterial conjunctivitis and Parinaud's oculoglandular syndrome. The latter has multiple causes including sarcoidosis, tularemia, secondary syphilis and cat-scratch disease. In each of these entities, unlike trachoma, the disease is sporadic rather than endemic within the community. A careful history, consideration of the epidemiological setting, appropriate cultures and serological testing will differentiate early chylamydial infection from these other forms of conjunctivitis.

Treatment

The failure to eradicate trachoma in endemic areas is a function of the inability to break the cycle of reinfection. Trachoma is a disease of poverty and its corollaries, crowding and poor hygienic conditions. Infection confers no immunity, and reinfection is inevitable in endemic areas unless there is improvement in the standard of living. It has been shown repeatedly that improvement in the economic and public health conditions reduces the prevalence and severity of trachoma within an endemic community.[144] No regimen using antibiotics alone has been successful.

Several antibiotics are available for topical and systemic therapy of trachoma.[7] Tetracycline, erythromycin, sulfonamides and rifampin have all been effective in population studies.[7,139,141,151,152]

Eradication programs must be directed specifically at school-aged children as they constitute the principal reservoir of the organism. Ideally, the whole community is treated. Orally given antibiotics are generally more successful than topical therapy.[151] Suggestive regimens include 2 to 4 grams of tetracycline or erythromycin taken orally each day for three to four weeks,[143] or tetracycline ointment three to four times a day for four to six weeks.[139] Intermittent, prolonged topical therapy (five days per months for six months) has also been successful.[139] With these therapies there is an improvement in the clinical activity of inflammation, reduction in ocular bacterial pathogens and variable reduction in density of organisms shown by fluorescent antibody staining of conjunctival scrapings.[143,145] As expected, suppression of disease is only temporary in hyperendemic, underdeveloped areas. Mass treatment has been most successful when associated with economic expansion, as has occurred in Taiwan. Topical steroids should not be used.[139] Prevention of blindness in adults also involves surgical correction of lid deformities and treatment of bacterial superinfections.[135]

Attempts to develop an effective vaccine against *C trachomatis* have been unsuccessful. Vaccines using a variety of antigenic preparations have produced only transient resistance to infection and a modest reduction in the intensity of established disease.[4,139] In addition, more severe inflammation may develop in vaccinated patients when rechallenged with the organism, presumably a result of induced hypersensitivity.[4]

Miscellaneous Infections

PHYLLIS A. GUZE, MD

Endocarditis

CULTURE-NEGATIVE ENDOCARDITIS due to *C psittaci* has been documented in the literature.[57,153,154] In two patients, the infection occurred on previously damaged valves and both patients died.[153] In one patient, urgent aortic valve replacement was necessary.[57] A more insidious course with subsequent mitral valve replacement was reported in the other case.[154]

Recently, a fatal case of culture-negative *C trachomatis* endocarditis in a young woman with a previously normal aortic valve was reported.[155] The retrospective diagnosis was made by detecting a 32-fold rise in the patient's IgM antibody using the micro-IF technique and by ultrastructural examination of the necropsy tissue. This is the first association of endocarditis with *C trachomatis*. Both *C psittaci* and *C trachomatis* should be considered in the differential diagnosis of infective endocarditis with negative cultures of blood specimens.

Reiter's Syndrome

It has been suspected for several years that chlamydial infection may be associated with Reiter's syndrome. *C trachomatis* has been isolated from the urethra, conjunctiva, synovial membrane or synovial fluid of patients with Reiter's syndrome,[1,156,157] and evidence for the frequent association of chlamydial infection with this syndrome has recently been presented.[158] In the genetically predisposed host, chlamydiae may be one of several agents that may initiate or make these patients more susceptible to the development of this syndrome.[1,159] Treatment of *C trachomatis* infection will relieve the infectious symptoms but will not reliably relieve the other manifestations of Reiter's syndrome.[5]

Other Infections

Chlamydial agents have been associated with *pharyngitis* in adults with inclusion conjunctivitis[160] and in one patient without ocular involvement.[161] *C trachomatis* has also been recovered following myringotomy of a patient with *otitis* and conjunctivitis,[162] and *hearing loss* has been documented.[134] Isolation of this agent from the *lower respiratory tract* of six adult patients who had pulmonary infection now raises the possibility of *C trachomatis*-associated respiratory disease in the adult.[163] Schachter[1] states that a simplistic approach may be to assume that any anatomic site containing columnar epithelial cells may be susceptible to chlamydial infection and disease, if a means of transmission exists.

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Chlamydial Infections

What Should We Do While Waiting for a Diagnostic Test?

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A SPECIALTY CONFERENCE entitled "Spectrum of Human Chlamydial Infections" precedes this editorial review.

Since the early 1970's an ever-increasing number of studies have associated *Chlamydia trachomatis* infection with various diseases and syndromes (Table 1). More recently, the prevalence of chlamydial infection has been assessed in larger-scale screening studies done chiefly in sexually transmitted disease (STD) clinics, prepaid health maintenance organizations, university student health services and obstetric/gynecologic clinics.[1-5] These studies indicate that the prevalence of chlamydial infection in both men and women generally exceeds that of gonorrhea in the same population, often by severalfold. In prenatal clinics, for example, *C trachomatis* has generally been isolated from 6 percent to 13 percent of pregnant women, and in studies where both chlamydial and gonococcal organisms were sought, the former has been two to seven times more common. In Seattle, screening of women seen at a student health service and at a family planning clinic have both shown chlamydial to gonorrheal infection ratios greater than 10:1. In our STD clinic, *Chlamydia* was isolated from the cervix of 18 percent of women being seen for new problems, while only 12 percent had *Neisseria gonorrhoeae* isolated. Young women (in 33 percent of women 15 years of age or younger, chlamydiae were found in the cervix), those using oral contraceptives, and those whose partners had nongonococcal urethritis (NGU) were at highest risk. We isolated *Chlamydia* from the urethra in 14 percent of heterosexual men attending our clinic, compared with a 12 percent prevalence for *N gonorrhoeae*. Serological surveys in venereal disease clinic populations indicate that 50 percent to 60 percent of heterosexual men and 70 percent to 80 percent of women have antibody indicative of prior chlamydial infection.

If chlamydial infections cause so many diseases and occur so frequently, why isn't more being done to diagnose, treat or prevent them? It may be instructive to consider this question from four different perspectives: those of (1) the infected patient, (2) the clinician seeing the patient, (3) the laboratory technician attempting to isolate *Chlamydia* and (4) the public health administrator. First, consider the patient's point of view. Unlike gonorrhea or genital herpes infection, chlamydial infection has received relatively little attention in the lay press, and, hence, most patients have not heard of it. The name itself cannot be easily pronounced or remembered and has not yet received popularized synonyms, such as "clap" for gonorrhea. Patients with an unfamiliar disease who have minimal or no symptoms may feel little motivation to seek treatment when named as a partner of an infected contact.

Assuming the patient seeks medical care because of symptoms, his or her interaction with the clinician rarely results in a specific diagnosis of chlamydial infection. In a man with overt urethritis, the diagnosis of NGU can readily be made on the basis of a Gram stain, and nearly all

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ABBREVIATIONS USED IN TEXT

NGU = nongonococcal urethritis
PID = pelvic inflammatory disease
STD = sexually transmitted disease

patients will receive appropriate empiric treatment with tetracycline. However, the cause of the illness generally receives little attention because the clinician cannot confirm by culture whether the patient has chlamydial or nonchlamydial NGU. Rather than initiating a time-consuming conversation that usually confuses the patient with unfamiliar names like *Chlamydia* and *Ureaplasma* and ends with the clinician admitting his inability to do a chlamydial culture for the patient, most clinicians soon conclude that such discussions are academic—thus, the patient is told he has NGU and receives empiric tetracycline. He learns nothing about *Chlamydia,* often does not receive advice about what should be done for his sexual partner or partners, and may even be given the impression that his condition is neither infectious nor sexually transmitted.

In comparison to dealing with a man who has NGU, however, it is even more difficult for a clinician to deal with symptomatic chlamydial infections in women. Unlike men with NGU, women with chlamydial infection do not often exhibit a characteristic clinical syndrome.[6] Further, we lack a simple diagnostic test, such as the urethral Gram stain for men, to make a syndromic if not causative diagnosis. Although women with chlamydial infections often have symptoms such as vaginal discharge, dysuria or lower abdominal pain, these characterize many other genital infections as well. Experienced clinicians may learn to recognize a combination of cervical edema, ectopy, friability and mucopurulent discharge as chlamydial cervicitis. Unfortunately, less than a third of all women with chlamydial cervical infection exhibit these signs[6] and, since they are often subtle, clinicians who have not had the opportunity to correlate their clinical findings with culture results generally have little confidence in basing a diagnosis (and treatment) on these signs. They have even less confidence in asking these women to refer their partners for examination and possible treatment, and rarely do so.

TABLE 1.—*Syndromes Associated With Sexually Transmitted* Chlamydia trachomatis *Infection*

Men	NGU, epididymitis, Reiter's syndrome, proctitis, lymphogranuloma venereum
Women	Mucopurulent cervicitis, bartholinitis, acute urethral syndrome, salpingitis, Fitz-Hugh–Curtis syndrome, lymphogranuloma venereum, postpartum endometritis, cervical cytological atypia, prepubertal vaginitis; postsalpingitis sequellae (such as infertility)
Neonates	Conjunctivitis, nasopharyngitis, pneumonia, otitis media, perinatal death (?)

NGU = nongonococcal urethritis

At present, most clinicians have no way to detect reliably asymptomatic chlamydial genital infections in men and women. Current evidence indicates that, in STD clinics, about a third of men with chlamydial urethritis and probably a half of women with cervical infection have no symptoms or have ignored symptoms. The likelihood of isolating *Chlamydia* from the urethra of an asymptomatic male is about 50 percent when two successive Gram stains a week apart show 4 or more polymorphonuclear leukocytes per 1,000× field.[7] However, such evaluation requires considerable patient cooperation and probably lacks sensitivity. In women, the cervical Gram stain has not been useful as a predictor of chlamydial infection. In summary, the clinician seeing patients with chlamydial infection is severely handicapped—there are no specific signs or symptoms that can be relied on in most cases, confirmatory diagnostic tests are lacking, cure cannot be easily assessed, asymptomatically infected patients cannot be reliably identified and treatment must often be on the grounds of ill-defined "suspicion." In addition, treatment for chlamydial infection generally involves at least seven days of an antimicrobial drug given four times per day. Compliance in patients with minimal symptoms and a diagnosis established without a confirmatory culture must certainly be suboptimal.

Many laboratory directors have been encouraged to provide chlamydial culture services to obviate some of the difficulties described above. *Chlamydia,* an obligate intracellular organism, is isolated most readily by tissue culture techniques. Traditionally, McCoy cells or HeLa 229 cells grown on coverslips in small (two-dram) vials have been used to isolate *C trachomatis.* Because tissue culture lines must be sterilely maintained and propagated, chlamydial cultures require a more elaborate laboratory facility than do cultures for *N gonorrhoeae.* The procedure also requires considerable technician time and, hence, costs much more ($20 to $50 laboratory cost per cul-

ture) than a gonorrhea culture (~$2.50 laboratory cost per culture). Even if cost were no object, transport of specimens for chlamydial isolation presents a problem. If refrigerated, the specimen must be inoculated onto prepared tissue culture monolayers within 24 hours of collection (the earlier the better), and must be kept cold during transport and until inoculation. Alternatively, specimens can be frozen at −70°C for an indefinite time, but this is not convenient in most hospitals or clinics and may result in decreased chlamydial titers. Finally, even in the best of circumstances, results of cultures may not become available for more than a week after the patient has been seen. Serodiagnosis using the microimmunofluorescent assay would obviate some of these problems, but in most clinical situations a positive serological finding does not have a sufficiently high predictive value for current infection, due primarily to the high prevalence of antibody from previous infection. Two exceptions are lymphogranuloma and infant pneumonia, both of which usually produce a characteristically high titer of antibody in the microimmunofluorescence test.

Finally, place yourself in the beleaguered position of public health officials who must determine how much money should be devoted to the diagnosis, treatment and prevention of chlamydial infection. The budget has been reduced, yet the law mandates that free services be provided for the diagnosis and treatment of gonorrhea and syphilis. Should culturing for this newer disease be undertaken, which might use nearly the entire budget? In which specific populations should specimens be obtained for culturing? Should the disease be reportable and, if so, only in patients with culture-confirmed cases? Should public health resources be devoted to tracing contacts of those with chlamydial infection, particularly contacts of women with pelvic inflammatory disease (PID), just as is done with gonorrhea and syphilis? If the disease is so often mild or even asymptomatic, can the expense of providing services be justified? How often do serious complications such as PID in women and epididymitis in men occur? Do the morbidity and mortality attributable to neonatal chlamydial infections justify screening of pregnant women? Does the apparent association of chlamydial cervicitis with cervical cytologic atypia justify screening of women in high-risk populations? More questions than answers present themselves to public health officials at this point. There is a critical need to define the long-term consequences of asymptomatic or subacute chlamydial infections—especially infertility, ectopic pregnancy, fetal wastage and relationship to cervical carcinoma—to provide clearer answers to these questions.

Obviously, a common thread running through the four perspectives outlined above is lack of an inexpensive, sensitive, and specific diagnostic test for *Chlamydia*. Although a microtiter isolation system permits processing of more specimens,[8] it does not solve the transport problem and still exceeds the cost of a gonorrhea culture by several fold. Alternative diagnostic tests for recognition of chlamydial antigens or chlamydial DNA in clinical specimens are being explored and may eventually provide the much-needed diagnostic test.

Until then, what should be done? Given the frequency and consequences of chlamydial infection, all physicians and health care clinics should have access to a laboratory where specimens for chlamydial culture can be sent. These referral laboratories should be available at least at the state level and, in larger cities, at the local level, and they should be supported at least partially by public funds. It is useful to examine the analogy of public support for gonorrhea culture testing during the past decade. Federal funding has been used to supplement state, local and private fee-for-service funding, and has led to widespread application of high-quality gonorrhea culture testing, leading to increased awareness by clinicians of the manifestations of this disease. A similar program is needed for establishment of facilities for chlamydial culturing. Referral clinics for STD should clearly have capabilities for *C trachomatis* cultures, to be used to confirm chlamydial infection in the following circumstances: (1) women with suspected mucopurulent cervicitis, salpingitis or both, (2) homosexual men with proctitis, particularly if gonorrhea-negative, (3) men with acute epididymitis, (4) sexually active women with dysuria, frequency and sterile pyuria, (5) those suspected of having lymphogranuloma venereum, and (6) infants with suspected chlamydial conjunctivitis or pneumonia. Although probably critical from a disease control standpoint, widespread screening to detect asymptomatic cases will not be feasible in many settings unless a cheaper test becomes available. However, female partners of men with NGU, whether chlamydial or not, should be treated empirically with tetracycline, as 30 percent to 40 percent will have

chlamydial cervicitis. Similarly, male partners of women with chlamydial cervicitis should also be treated empirically. In women and heterosexual men with *N gonorrhoeae* infection, coinfection with *C trachomatis* occurs in 30 percent to 50 percent and 15 percent to 25 percent, respectively. In reliable patients, clinicians should consider using tetracycline rather than single-dose ampicillin or parenteral penicillin, because the latter two drugs usually will not eradicate *Chlamydia*. Contact tracing of nongonococcal, as well as gonococcal, PID should be implemented now. Until a less expensive test becomes available, testing of all pregnant women for *Chlamydia* may be premature, although the evidence for the importance of *Chlamydia* in perinatal infections is becoming hard to ignore. However, screening of high-risk pregnant women (unmarried, adolescent, nonwhite) may be advisable now in view of the possible consequences of infection during pregnancy. Finally, clinicians and public health authorities should try to educate patients about chlamydial infection whenever possible, even if the diagnosis cannot be confirmed by culture.

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EDITORIALS

Thoughts on Medical Education

One can have an uncomfortable feeling that the medical profession may not be as efficient or as effective as it could be in fulfilling its responsibilities to patients, a health-seeking public or society as a whole. Too many patients are seeking help outside the profession in order to feel better. There is increasing public support for expanding the scope of practice of other professionals in the field. No one seems to be functioning adequately in the much needed role of physican to society at large. Could it be that the medical education enterprise has not kept pace with the rapidly evolving needs and responsibilities of the profession?

The worlds of medical science and medical practice have become enormously more complex. It has been decades since anyone could hope to master all of medical knowledge, and the useful half-life of what can be learned has been estimated at only five or ten years. The proliferation of science and technology has led to significant specialization and subspecialization in the health care field, both within and outside the profession of medicine. The results of this are only just beginning to be apparent. Little attention has been given to all the relationships among these professional and nonprofessional specialists and subspecialists, and to how they might relate to the oneness of medicine and the wholeness of individual patients in patient care. Then, as medical science and technology have become more complex and able to do more (often at an increased risk), costs have risen greatly, both costs of care and costs of litigation and compensation when harm instead of cure happens. The ramifications of cost have added many new dimensions and much new complexity to the world of medical practice and has brought many new kinds of professionals and many new disciplines to the health care scene. The problems so engendered now occupy much of the time and energy of individual practitioners as well as professional leaders who are all finding themselves caught up in the intricacies of interprofessional tensions, the poorly understood economic problems of health care, and various initiatives and interventions imposed by no doubt well-intentioned governments in behalf of the public. Physicians have not been prepared by their education and training to deal with complexities such as these, let alone to guide their evolution toward rational solution in the interest of patients, a health-seeking public or society as a whole.

If there were to be a new look at medical education what might one see? The principal purpose for medical education has to be to provide the education and training physicians need for leadership and effectiveness in medical practice and patient care, and this is becoming increasingly complex and is changing all the time. What seems to be needed is a more balanced educational fare of science and technology; caring and curing; skills in communications and interpersonal and interprofessional relations; and much more attention to physical, social, economic and political factors in the external environment as these may affect illness and health, influence medical practice and have impact on patient care. Then the realities of increasing complexity and ever present change also suggest that the education and training of physicians should be a much more integrated and continuous process that it is at present.

In a sense a physician's education and practice both undergo a progressive differentiation. In medical school an overview of the whole or a framework for future knowledge, skills and practice experience is provided. Residency training focuses on a specialty, but at its best still relates to the whole of medicine. And later, as each physician develops an individual practice interest and experience, education and training should be refined to meet the needs of this much more differentiated practice. But since medical science and technology remain a whole and since patients should be viewed and treated as whole persons interacting with their external environment in health and disease, there is need for practicing physicians also to keep current with progress in their specialty and indeed with the capabilities and limitations of all the specialties relating to health care. Thus while differentiation in learning and practice occurs, it still remains part of and interacts with the whole.

It would seem that there are some corollaries to this: (1) Medical education cannot cover everything in depth but there must be an awareness of the whole at every level of differentiation, only in the depth necessary for that level of differentiation. (2) Medical education is a continuum extending throughout a professional life, and if this is so there should be more overlap and interaction at all levels of differentiation. (3) Since within the whole of science and practice each physician becomes differentiated, there should be a focus on individual learning skills, on methods of information transfer and retrieval, on learning and information resources, and on developing and refining problem-solving skills throughout the continuum of medical education, so that in a sense each physician becomes something of a self-directed learner at each level of differentiation of practice. (4) The human aspects of medical practice, including relationships with other professionals, human relationships within the framework of patient care and the care of patients as whole persons should also be stressed throughout the continuum of medical education.

If medical education is to become a better instrument to help practicing physicians and the medical profession as a whole to be more efficient and effective in fulfilling responsibilities to patients, the health-seeking public or society at large, it seems likely that some changes will be needed. This will require some closer interaction between the professional and educational parties at interest. The Coordinating Council on Medical Education has recently been succeeded by a high-level Council on Medical Affairs which has the capability of involving many of the parties that might be expected to have an interest in this at the national level. Clearly, some such coordinating and facilitating body would be needed.

—MSMW

New Americans—New Diseases?

SINCE 1975 the United States has accepted over 500,000 Indo-Chinese refugees and 150,000 non-Indo-Chinese from Southeast Asia. Since April 1980 some 175,000 Cuban and Haitian immigrants and refugees have entered the country. The Southeast Asian refugee flow continues at 12,000 to 14,000 per month, along with several thousand Cuban, Haitian, Soviet, Eastern European, Near Eastern, Latin American and African immigrants and refugees. About 232,000 refugees entered the United States in 1980, 78 percent of whom were Indo-Chinese.

In California there are over 160,000 Indo-Chinese, excluding illegal aliens and migrants. In 1980, the number of new immigrants was about 50,000 with some 5,000 persons per month settling in the state, many being returnees from other states. California's current share is 35 percent to 40 percent of all US refugees and growing. Undocumented aliens, immigrants and other classes of newcomers in California number in excess of several million. (Mannino JD: Fact Sheet: Refugees. Office of Refugee Affairs, San Francisco Department of Social Service, Unpublished report, Feb 3, 1981)

The report by Mannino estimates that in San Francisco about 500 Indo-Chinese find a new home each month—some 25,000 so far—which is a larger group than in all but two other states, though it is only the third or fourth largest Indo-Chinese refugee community in California. Punjabi communities totaling several thousand immigrants have come to California, moving to the northern Sacramento Valley in Sutter and Yuba counties,

"Intestinal Protozoan Infections: Prevalence in the San Francisco Bay Area," by Edward K. Markell and Ruby A. Kuritsubo appears elsewhere in this issue.

while large groups of Yemini have settled in the San Joaquin Valley in Delano, California. The massive Chicano-Latino immigration into Southern California and the sun-belt border states has produced dramatic and permanent demographic and sociological change with far more to come.

What can we expect with regard to imported disease? Will malaria return to California, where it was a scourge of miners a century ago, being known as the "goldminer's disease"? In addition to malaria, still the world's most lethal infectious disease, can we anticipate local outbreaks of active tuberculosis, cholera, hepatitis, leprosy, amebic dysentery, giardiasis, ascariasis, strongyloidiasis, trichuriasis, hymenolepiasis, taeniasis and cysticercosis, fasciolopsiasis, schistosomiasis, clonorchiasis, heterophyiasis and paragonimiasis? Should we batten down the hatches and prepare for a storm of exotic diseases? In a word: *NO*. Levels of infection among newcoming residents vary widely, depending on the origin, experience and individual condition of these persons. The "exotic" diseases are in large measure unfamiliar rather than foreign. We already have sizable populations of the soil-borne nematodes *Ascaris, Trichuris, Necator* and *Strongyloides*. We have *Toxocara* and *Toxascaris* in our dogs and cats, *Taenia saginata* in our cattle, *Taenia solium* in our pigs, *Hymenolepis* in our rats. What is lacking in this country and, therefore, truly exotic (and tropical for the most part) are vector-borne infections whose range is strictly dependent on the abundant availability of specific vector or intermediate host species—even strains—as well as a large reservoir of infected humans, or animals in some instances. Schistosomiasis, found throughout Africa and the Middle East, as well as the Orient, certain Caribbean Islands and South America, cannot be sustained without the correct host snails—which are found in South America but are absent from the United States. About 30 percent of the new Americans from Yemen are infected from their homeland,[1] but in this country the disease will remain with them. Filariasis, with its textbook horrors of elephantiasis, depends on specific mosquito strains and a human infection source. African sleeping sickness, or trypanosomiasis, requires human-feeding tsetse flies, which are restricted to Africa. South American trypanosomiasis or Chagas' disease requires reduviid or cone-nosed bugs. Not just *any* form, but certain species and strains that defecate while feeding, as the infectious agents must be scratched into the eyes or mucous membranes from feces passed while the bugs quietly take their blood meal. Vector species are found in the United States and a few cases of endemic Chagas' disease have been reported, but the US bugs have somewhat better table manners—or toilet training. They defecate a few minutes *after* feeding (and leaving the host).

Malaria, once endemic in this country, infecting some 6,000,000 a year, chiefly in the southeastern states, is a marginal danger at worst. Potential *Anopheles* vector mosquitoes do indeed reside here, such as *A freeborni* in California. With fiscal retrenchment and loss of Mosquito Abatement District funds, we may find mosquito numbers far from abated, and increasing. The worst-case possibility might well apply here. Approximately a fourth of the new settlers from India and Pakistan had malaria on entry,[2] and a thousand or so cases of malaria are brought into this country annually from Southeast Asia and elsewhere.[3] Many are not reported or discovered (or they are misdiagnosed by nonmilitary or nonpublic health physicians, who generally are unfamiliar with the disease). A dozen instances of local or autochthonous spread of malaria have been reported in the United States since the famous episode in 1952 when a Marine veteran from the Korean war, camping at Clear Lake, California, passed his malaria via local *Anopheles* mosquitoes to 35 girls at a Brownie camp nearby. And malaria is indeed present among the Southeast Asian immigrants and refugees as well as among the Pakistanis. Perhaps 10 percent of some groups, especially among Laotians and the Hmong people from the highlands, have evidence of past infection if not overt disease. Other cases may be only repressed by prior partial treatment. If the infection is due to *Plasmodium falciparum* organisms (this is the only life-threatening form of malaria), further problems are to be anticipated, owing to the widespread distribution of chloroquine-resistant falciparum malaria throughout Southeast Asia[4] (as well as parts of Latin America). So much for the worst-case scenario. Spread of imported malaria to local populations still remains unlikely. The required combination of massive breeding of suitable *Anopheles* mosquitoes, a large reservoir of untreated human infections, a nearby population of those without immunity, especially children, and the likelihood that this chain will remain unbroken for a sustained period is a set of circumstances that is unlikely to develop. The alarum that will be raised when outbreaks occur,

the availability of mosquito control measures, rapid treatment of active cases, and excellent epidemiological resources to survey other exposed populations and to seek out cases for treatment would quickly extinguish a malaria fire and alert the populace.

However, problems *do* exist—chiefly the need for consciousness-raising: increased physician awareness, accompanied by a dusting off of long-neglected tropical medicine texts and course notes in parasitology; medical surveillance of the newcomers; improved clinical diagnoses along with increased readiness of diagnostic laboratories to deal with imported parasitic infections; availability of prompt and appropriate treatment, assisted by information from experts at the Centers for Disease Control (telephone (404) 329-3676 or 3670 for drug services). Some infections are long-lasting and difficult to treat, clonorchiasis being an example that many Chinese can attest to, even 30 to 40 years after leaving China or Taiwan. Giardiasis can be long-lasting and nonresponsive to treatment. Strongyloidiasis is sometimes chronic and is potentially lethal following immunosuppression. Vivax malaria can relapse for up to five years after an initial bout. Malariae malaria can recrudesce from low-level blood stream infections for several decades. These, however, are individual, *private,* not *public* health problems. The danger is not to resident Americans but to the newcomers themselves. Especially in danger are those whose levels of exposure have been greatly increased and whose resistance to infection has been reduced concomitantly by their personal tragedies and unbelievable suffering, including long periods of malnutrition or even starvation, crowded conditions in refugee camps with little or no protection against fecal contamination, and the psychic stress of war, uprooting, deprivation and loss, followed by entry into a strange and frightening new environment. It is hardly surprising that parasite loads are sometimes so high, affecting 50 percent or more of their numbers.[5-10] But fortunately most intestinal worms are easily treated.[11] Malaria, in spite of chloroquine resistance, can be cured. It is the conditions of life that control exposure and determine infection levels: sanitation, water supply, housing, crowding and nutrition. Intestinal infections of agricultural workers in many rural camps exceed those of the refugees, particularly levels of amebiasis. *How* one lives as well as *where* one is—or was—are the prime factors. Immigration barriers will not control endemic infection levels—sanitation, reasonable housing, clean water, adequate nutrition and education *will.* Past mistakes engender future problems, to be faced by our children and those of the war-ravaged refugees from Southeast Asia living new lives in this country. Sympathetic recognition and understanding of their suffering, loss and need will help them through their initial culture shock. Personal health care will clear the parasites with minimal need for concern for endemic neighbors. Then will come the period of adaptation, integration and new citizen status, to be followed by productivity and contributions by these hard-working, responsive and culturally ancient new Americans.

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Prevention of Nuclear War

NUCLEAR WAR is patently insane from the standpoint of the health and well-being of humanity and one would like to think that all those who come into possession of a destructive thermonuclear capability will always be sane enough not to use it. But the fact is that insanity has not been unheard of among the world's rulers, although so far none of those obviously affected have had thermonuclear weapons at their disposal. Unfortunately there is clear evidence that more and more nations are developing nuclear armaments presumably for defense against other nations which might attack them with these kinds of

weapons. It seems inevitable that some disturbed group or nation somewhere will use these weapons as a last resort or in the belief that their use will prevent something worse. And again it should be remembered that those in charge of the group or nation may not always be entirely sane.

There is a growing sentiment among many physicians that somehow the medical profession should do something to bring some sanity into the worldwide approach to the proliferation of nuclear armaments or the capability of developing them. The medical profession can speak authoritatively on their short-range and long-range impact on health, and the profession is represented in every nation on earth. It is also the profession most expert in what little is known of the cause, diagnosis and treatment of insanity. An effective course of action by the profession, as physician to the world so to speak, is sorely needed, but is not yet identified.

An initial step was taken recently by the House of Delegates of the American Medical Association which recommended that an agenda item at the next meeting of the World Medical Association Council be a discussion of the medical consequences and prevention of nuclear war. All physicians and even all of humanity can hope that these discussions will lead to some practical steps that can be taken by physicians and others around the world.

—MSMW

EDITOR'S NOTE: A medically sponsored World Disarmament Campaign is also under way. Physicians wishing more information about this may contact André Bruwer, MD, 4122 East 6th St., Tucson, AZ 85711.

CASE REPORTS

Refer to: Tolle SW, Cartwright CA, Parthemore JG: Innominate vein obstruction caused by intrathoracic goiter. West J Med 135:235-238, Sep 1981

Innominate Vein Obstruction Caused by Intrathoracic Goiter

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BENIGN INTRATHORACIC GOITER is a rare cause of innominate vein obstruction severe enough to cause the clinical features of the superior vena cava syndrome. In 1967 Kamiya and colleagues[1] published a review of 734 cases of superior vena cava (SVC) syndrome reported since 1949. Only 9 of the 734 were caused by benign intrathoracic tumors. Of these nine, four were caused by intrathoracic goiter. These four included two cases reported by Calkins[2] and two cases reported by Effler and Groves,[3] who subsequently reported a third case.[4] Other single cases of SVC syndrome caused by intrathoracic goiter have been described by Silverstein and co-workers,[5] Steenerson and Barton,[6] Sherman and Shahbrahrami,[7] McIntire and Sykes,[8] Hillerdal and colleagues,[9] Lesavoy and associates,[10] Nishikawa and co-workers,[11] and Sparagna.[12] This comprises a total of 13 cases.

The excellent functional status as well as unimpaired long-term survival of the patients with a benign cause of the SVC syndrome is emphasized in the 1962 report from the Cleveland Clinic, in which 16 patients with nonmalignant causes were followed for five to ten years.[3] The extensive development of collateral veins permitted excellent adaptation.

Our case report further substantiates the benign course of patients with intrathoracic goiter as the cause of the venous obstructive syndrome and indicates the usefulness of thyroid scanning before contrast studies in those patients whose history strongly suggests a benign cause or fails to provide a readily identifiable explanation for an SVC syndrome. To our knowledge, this represents the first reported case of an SVC syndrome induced by intrathoracic goiter in which clinical improvement was associated with thyroid hormone therapy alone.

Report of a Case

A 71-year-old man was admitted with complaints of pain and swelling of the left hand of two years duration, which had progressively increased over the two months before admission and were unresponsive to administration of ibuprofen (Motrin), 400 mg four times a day. His wife had noted neck and facial fullness, as well as dilated veins over his anterior chest, for several years before admission. However, there had been no noticeable change in recent months. The patient stated that he had not experienced loss of weight, stridor, shortness of breath, hemoptysis or change in a minimally productive chronic cough.

His past medical history was remarkable for stage C prostatic adenocarcinoma, treated with local radiation. Subsequent bone scans were negative. He had a history of left-sided podagra, successfully treated with colchicine, and hypertension treated with triamterene and hydrochlorothiazide (Dyazide). He had a history of smoking 1½ packs of cigarettes a day for 40 years (60 pack-years), with clinical evidence of pulmonary disease for which he was treated with aminophylline.

On physical examination it was noted that he was a plethoric, obese male with facial cyanosis and fullness, prominent jowls and a thick neck. Prominent dilated tortuous vessels were seen over the right anterior side of the chest and right upper arm. He was afebrile with a blood pressure of 128/76 mm of mercury, a pulse of 80 beats per minute and respiration rate of 18 breaths per minute, unlabored. Fullness was noted in the

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Submitted January 7, 1981.

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supraclavicular fossae bilaterally. He had bibasilar rales that cleared with coughing. A fourth heart sound was noted and the liver span was 12 cm. The prostate was not palpable. Erythema, tenderness and pitting edema were noted over the dorsolateral left hand, maximal at the fifth metacarpophalangeal joint.

Routine laboratory evaluation was unremarkable except for the following: creatinine 1.6 and uric acid 10.4 mg per dl. Other values included thyroxine 11.5 μg dl; triiodothyronine resin uptake of 36.7 percent; free thyroxine index 4.22, and thyroid-stimulating hormone 4.4 μU per ml.

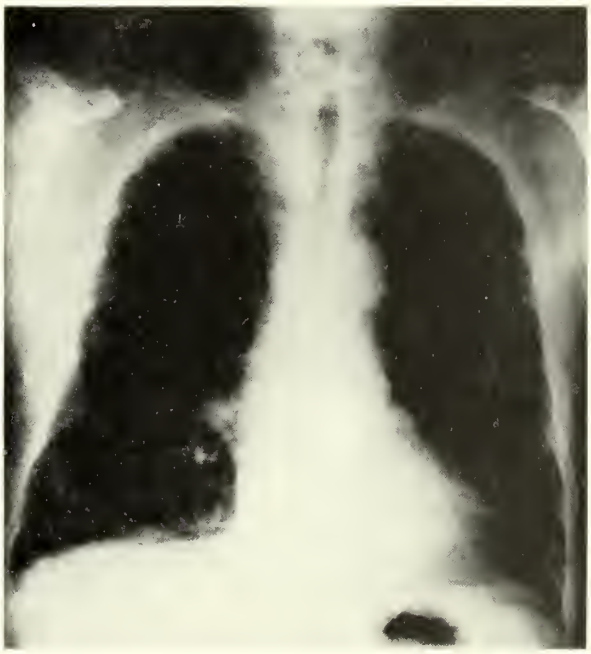

Figure 1.—A roentgenogram of the chest, at the time of admission, shows significant superior mediastinal widening with narrowing of the trachea.

Figure 2.—Computed tomogram at the level of the midmanubrium that shows a mass encircling the trachea. The entire study showed the mass to extend from the neck downward to the level of the aortic arch.

A roentgenogram of the chest showed significant superior mediastinal widening, with narrowing of the trachea (Figure 1). Review of previous chest roentgenograms showed the mediastinal widening and tracheal narrowing had progressed gradually over two years.

Gout of the left fifth metacarpophalangeal joint was confirmed by observation of urate crystals in the joint fluid aspirate. The hand symptoms responded promptly to colchicine and indomethacin therapy.

Computerized tomography showed a mass encircling the trachea and extending into the neck (Figure 2). A superior venocavagram confirmed a superior mediastinal mass with lateral displacement and irregular narrowing of the right subclavian and both innominate veins. There was a prominent right lateral thoracic collateral vein (Figure 3). Bronchoscopy demonstrated 50 percent extrinsic narrowing of the trachea, with no endotracheal lesions.

Mediastinoscopy and biopsy were carried out. Histopathologic findings were those described for benign nodular goiter. A ^{131}I thyroid scan, deferred a month because of earlier administration of iodinated contrast substances, showed heterogeneous uptake throughout the mass, consistent with nodular goiter. Thyroid hormone therapy (thyroxine, 75 μg a day) was instituted, with sig-

Figure 3.—Venocavagram showing a superior mediastinal mass partially obstructing both innominate veins. A prominent lateral thoracic collateral vein is noted on the right anterior side of the chest.

nificant improvement reported in clinical symptoms after two months.

Discussion

The SVC syndrome is caused by malignancy in more than 90 percent of recently reported cases.[13,14] Of these cases, 75 percent to 80 percent have been attributed to bronchogenic carcinoma, 12 percent to 15 percent to lymphoma, 6 percent to 7 percent to metastatic cancer; only 3 percent have had benign causes. The predominance of malignant lesions as the cause for the SVC syndrome was not reported in earlier series. Before 1949, in a series of 524 cases reported by McIntire and Sykes,[8] only a third of the cases of SVC syndrome were caused by primary intrathoracic malignant lesions, while an equal number were attributed to aortic aneurysms. The increase of thoracic malignancy as a cause of the SVC syndrome became apparent in the literature review of Kamiya and colleagues,[1] which spanned 1949 to 1967 and included 734 patients of whom 540 (73 percent) had thoracic malignant lesions. This observation has been attributed not only to the pronounced increase in primary lung cancer, which has occurred during this period, but also to the decreased incidence of both syphilitic aortitis and granulomatous mediastinitis, the latter most often caused by tuberculosis or histoplasmosis.

Benign causes for the SVC syndrome were and are extremely uncommon. They include intrathoracic goiter, idiopathic sclerosing mediastinitis, granulomatous mediastinitis, aortic aneurysm, aortovenous fistula, idiopathic thrombosis of the SVC, and a considerable increase recently in procedure-related SVC thrombosis associated with Swan-Ganz catheters, pacemakers, subclavian catheters and so forth.

The SVC syndrome, when caused by a malignant lesion, usually presents with a history of recent onset of swelling and fullness of any, or a combination, of the following: conjunctivae, face, neck and torso. Plethora or cyanosis as well as dilated vessels over the upper thorax may be seen. This may progress to include symptoms of cerebral edema such as headache, visual distortion, confusion and altered consciousness. The mean life expectancy, even with therapeutic intervention, is only 3.9 months.[13] This presentation differs greatly from that seen in patients with an SVC syndrome that has a benign cause. In the latter, the symptoms are usually gradually progressive and, in most instances, limited. Survival is prolonged and rarely influenced either by the SVC syndrome or its cause. Effler and Groves[3] reported 16 patients with SVC syndrome of benign causes, who received no therapy and were followed for five to ten years. Of their 16 patients, 7 had presumed granulomatous mediastinitis and 2 had presumed intrathoracic goiter. They noted a gradual diminution in the severity of their patients' clinical symptoms and attributed this to the development of collateral veins.

Our patient was euthyroid clinically and chemically. This is typical of the reported cases of SVC syndrome induced by an intrathoracic goiter. Such goiters have been described as multinodular and of massive size. In our patient, diagnostic thyroid scanning was delayed a month by the prior administration of iodinated contrast materials. Thyroid imaging should be done before other iodinated contrast studies in those patients in whom SVC syndrome has been insidious in onset, suggesting a benign cause, or in those in whom a malignant condition is not immediately suspected. Such imaging may provide information that will prevent the patient from undergoing a surgical procedure with its attendant risks, particularly that of severe bleeding related to increased venous pressure and vascularity. When surgical bleeding has occurred, ligation of collateral veins has frequently been necessary to secure hemostasis.

Most of the reported cases of SVC syndrome induced by an intrathoracic goiter have been treated by total or subtotal thyroidectomy.[5,6,9,10] In these cases, the operations relieved the SVC syndrome. We were unable to identify any reports of patients treated solely with thyroid hormone. In light of the clinical response of our patient to thyroid hormone therapy and the excellent prognosis of the untreated patients with SVC syndrome that has a benign course.[3,4,15] It seems reasonable to administer thyroid hormone therapy to patients with SVC syndrome caused by an intrathoracic goiter in which neither bleeding nor malignant lesions appear to play a role. Patients treated in this manner will, of course, require monitoring for relief of clinical symptoms, as well as for the possible onset of thyrotoxicosis.

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Refer to: Fischer MD, Hopewell PC: Recurrent pulmonary emboli and Buerger's disease. West J Med 135:238-241, Sep 1981

Recurrent Pulmonary Emboli and Buerger's Disease

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THROMBOANGIITIS OBLITERANS (Buerger's disease) is a relatively rare, chronic vasoocclusive disorder characterized by intermittent but progressive vascular, primarily arterial, insufficiency in the extremities.[1,2] Visceral involvement is fairly common with lesions being found in arteries of the renal, coronary, mesenteric and cerebral circulatory systems that lead to thromboses and ischemia in these organs.[3-7] Superficial and deep venous involvement has also been recognized since the original description of this disease by Buerger in 1908.[1] However, we have not found a reported case of pulmonary vascular involvement or pulmonary thromboemboli from venous thromboses diagnosed during life.[8] In the case reported here, the initial clinical manifestation of Buerger's disease was an acute pulmonary embolus.

Report of a Case

A 25-year-old man was admitted to San Francisco General Hospital Medical Center in March 1972 because of pleuritic pain on the right side of the chest associated with dyspnea and cough productive of blood-streaked sputum. During the week before admission, the patient had noted swelling and pain in his left calf. There was no history of trauma, previous venous disease or pulmonary disorders. He was taking no medications at the time of admission and had smoked two packs of cigarettes a day for five years (ten-pack years). His only previous medical problem was that of anhidrotic ectodermal dysplasia. A physical examination showed a well-developed man with characteristic features of anhidrotic ectodermal dysplasia and moderate respiratory distress. The pulse was 140 beats per minute, blood pressure 122/70 mm of mercury, respiration 40 breaths per minute and temperature (oral) 38.3°C (101°F). The lungs were clear on percussion; there were no rales, rhonchi or wheezes, but a pleural friction rub was heard over the posterior base of the right lung. There was augmentation of the pulmonic component of the second heart sound but no other cardiac abnormalities. There was mild tenderness in the right upper quadrant of the abdomen and bowel sounds were hypoactive. All peripheral pulses were symmetric in magnitude. Examination of the extremities showed swelling and tenderness of the left calf and Homan's sign; there was a palpable cord in the distribution of the saphenous vein. No other abnormalities were found.

Laboratory tests showed normal values for hemoglobin, leukocyte count and serum electrolyte levels. The electrocardiogram showed a heart rate of 130 beats per minute, an axis of positive 110°, and incomplete right bundle branch block. The roentgenogram of the chest showed no abnormalities. Arterial blood gas tensions with the patient breathing room air were Po_2 50 and Pco_2 38 mm of mercury, and pH 7.39. Perfusion lung scan using technetium pyrophosphate macroaggregated

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Supported in part by National Heart, Lung, and Blood Institute grant HL-19115 (Pulmonary Vascular Disease SCOR).

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albumin showed multiple bilateral segmental defects (Figure 1A).

The diagnosis of multiple pulmonary emboli and deep vein thrombophlebitis of the left leg was made. Heparin therapy was begun, and during the next seven days, dyspnea and chest pain disappeared. The swelling and tenderness in the left calf improved. Warfarin therapy was substituted and continued after discharge.

In April 1972 the patient was readmitted because of pain and resulting claudication in the left foot. At that time, a physical examination and arteriography documented severe bilateral arterial occlusive disease of the lower extremities. A perfusion lung scan done at that time showed resolution of previously seen defects (Figure 1B).

During the next six years, the patient was readmitted to hospital on several occasions for episodes of thrombophlebitis of the upper and lower extremities. Recurrent episodes of acute dyspnea and pleuritic chest pain were treated as pulmonary thromboemboli. Pulmonary angiography was not done because of the clear-cut presence of venous disease, which in itself was an indication for anticoagulant therapy, and because deep vein thrombophlebitis worsened after a femoral arteriogram. The patient's noncompliance with taking medication as directed made long-term warfarin therapy difficult. Results of serial pulmonary function tests are summarized in Table 1.

TABLE 1.—*Data on Pulmonary Function*

Date	*FEV_1/FVC (Percent)*	*VC (Liters)*	*TLC (Liters)*	*DLCO (ml/min/mm of mercury)*
May 1973	82	4.9 (93)*	5.9 (82)	24.9 (71)
Sept 1974	86	4.7 (90)	5.7 (80)	24.3 (68)
Sept 1979	83	4.2 (82)	6.1 (85)	22.7 (67)

FEV_1/FVC = percent of the forced expiratory volume in the first second to forced vital capacity; VC = vital capacity; TLC = total lung capacity; DLCO = diffusing capacity for carbon monoxide.

*Numbers in parentheses represent percent predicted.

Symptoms of arterial insufficiency were minimal until August 1978, when the patient was again admitted to the hospital because of severe pain in the right lower extremity. At that time, he had evidence of severe arterial insufficiency in the right lower leg and foot. Right lumbar sympathectomy was done, but because of intractable pain and failure to improve postoperatively, the right leg was amputated below the knee. Microscopic ex-

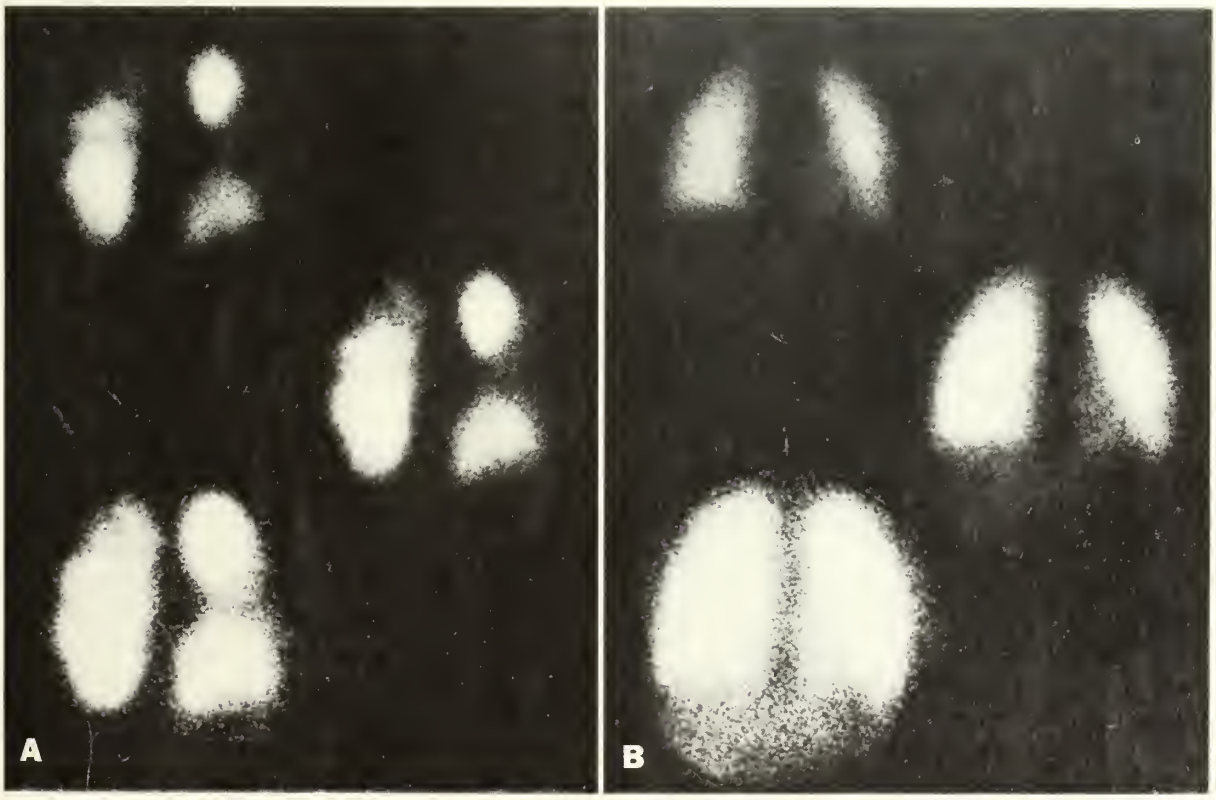

Figure 1.—A, Anterior view of initial perfusion scan (3/1/72) showing bilateral defects; **B,** perfusion scan six weeks later showing resolution of perfusion defects.

amination of the vessels in the amputated leg showed arterial and venous inflammation diagnostic of Buerger's disease (Figure 2).

After a bus trip from Texas in July 1979, the patient was readmitted to hospital with complaints of pain in the left calf and severe pleuritic pain on the left side of the chest associated with dyspnea. There was no history of fever or sputum production. Findings of a physical examination included mild respiratory distress, blood pressure of 120/80 mm of mercury, pulse 110 beats per minute and respiratory rate 20 breaths per minute. Decreased breath sounds, dullness to percussion and a pleural friction rub were noted over the left lower thorax. There was evidence of swelling, erythema and tenderness over the left calf. A roentgenogram of the chest showed radiodensity in the left lower lung zone. A xenon 133 ventilation study and a perfusion lung scan, using macroaggregated albumin tagged with technetium 99, showed a normal distribution of ventilation and a large segmental perfusion defect in the left lower lobe (Figure 3). Heparin therapy was begun and the patient improved during the next two weeks. He was discharged after resolution of the left lower extremity inflammatory process.

Figure 2.—Section of neurovascular bundle from amputated leg. Note organizing thrombi in both the large vein and adjacent smaller arteries (elastic van Gieson stain; reduced from original magnification ×12.5).

Discussion

The cause of Buerger's disease has not been determined. Toxic or infectious causes do not seem to play a role in the pathogenesis of this syndrome, but heavy cigarette smoking is noted in most cases. Increased affinity of hemoglobin for oxygen secondary to the higher carboxyhemoglobin levels of smokers has been suggested as contributory. Also, tests showing abnormal thromboplastin generation and elevated heparin precipitable fraction of fibrinogen have implied a thrombotic cause. This syndrome is probably caused by more than one factor, but heavy cigarette smoking appears to play a central role.[9]

We have not found reports of pulmonary vascular involvement in living patients with Buerger's disease. In 1940, Hausner and Allen[3] described a young man with clinical evidence of insufficiency of the deep venous system of both lower extremities who died after an episode of chest pain. At postmortem examination, a partially occluded pulmonary artery was found. Microscopic examination showed pronounced inflammatory reaction in the pulmonary vessel wall with a closely adherent, highly cellular mural thrombus. This was considered diagnostic of thromboangiitis obliterans.

Our patient has pathologically established arterial and venous involvement with Buerger's disease. In many respects, he is typical of patients with this disease. The age at the time of onset is generally in the range of 20 to 40 years old.[10] As is invariably the case, our patient is a heavy smoker. He has severe progressive arterial insufficiency involving large vessels, especially in the extremities. Microscopic examination of sections of the amputated leg showed characteristic abnormalities: intense transmural inflammation of both arteries and veins interspersed with normal segments of vessel.

Although we do not have angiographic proof of recurrent pulmonary emboli, the combination of clinical and physiological evidence plus the

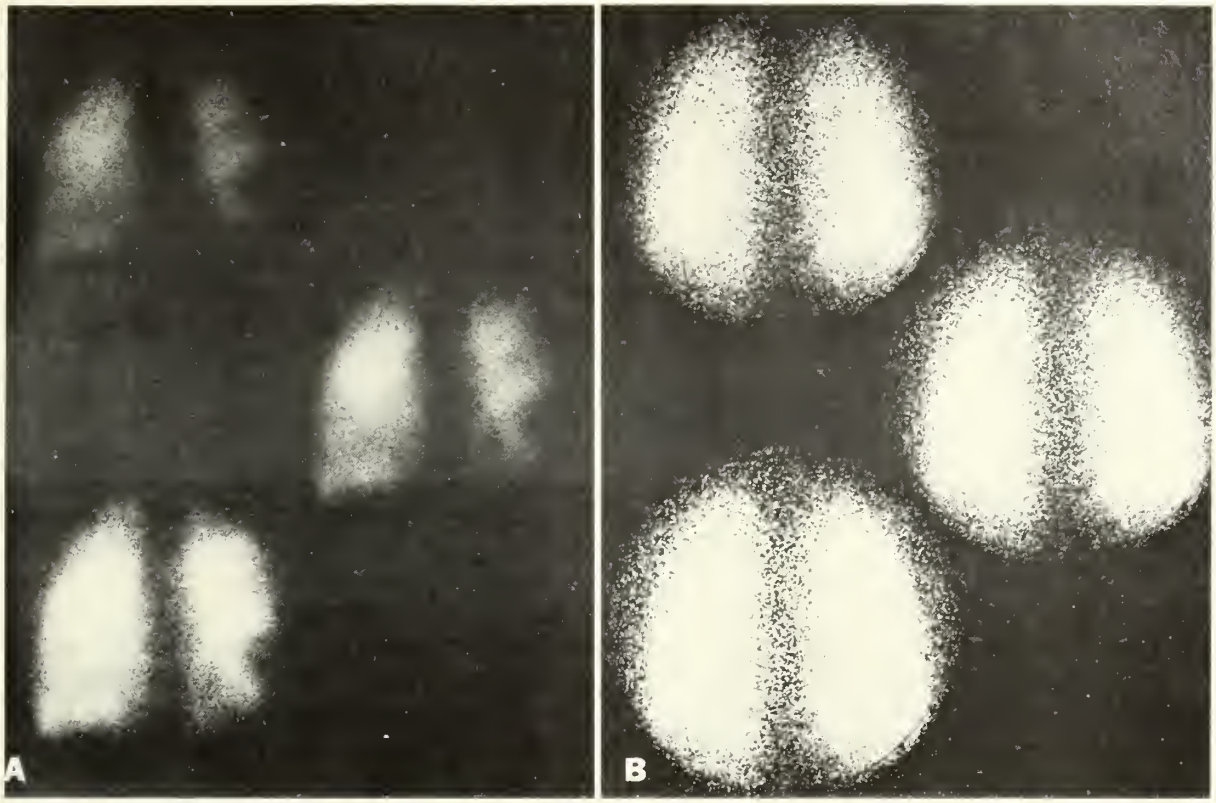

Figure 3.—A, Perfusion scan showing defect in left lower lobe; **B,** corresponding ventilation scan in equilibrium phase shows no abnormalities.

"high-probability" lung scans—without an alternative explanation—provide persuasive evidence of this complication.[11] Likewise, local thrombosis secondary to an inflammatory process of the pulmonary vessels was not excluded. The persisting reduction in pulmonary-diffusing capacity for carbon monoxide suggests that a significant portion of the pulmonary vascular bed has been obliterated either by thromboembolic occlusion or primary vascular involvement.

The frequency with which pulmonary vascular involvement occurs in patients with Buerger's disease is not known. The occurrence of pulmonary involvement in our patient suggests, however, that this may be an important and potentially life-threatening manifestation of thromboangiitis obliterans.

Summary

This report describes a young man who had phlebitis of the deep veins of the leg and pulmonary emboli when first seen. Subsequently, these proved to be initial manifestations of Buerger's disease. The early course was dominated by recurrent episodes of pulmonary embolization before development of typical systemic arterial occlusions. To our knowledge this presentation of Buerger's disease has not been reported previously.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Gastrointestinal Barotrauma in Scuba Divers

To the Editor: I was most interested in Dr. Kenneth Kizer's report[1] on gastrointestinal barotrauma in scuba divers.

The symptoms described by Dr. Kizer are seen relatively infrequently apart from the abdominal fullness. However, he fails to point out one particular condition which would be of a more urgent and serious nature. This occurs when a diver has an inguinal or other type of hernia and intestinal gas escapes into the hernial contents. On ascent, this condition may very well produce incarceration or strangulation of the hernia. For this reason, it is important to inform all divers known to have a hernia of this inherent risk. Physicians caring for patients with this problem should be informed of the nature of the injury and the method of reducing this by hyperbaric treatment; or, if diving facilities are available, they should be made aware of the technique for reduction of hernia in descent.

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Member, National Association of Underwater Instructors
Associate Clinical Professor of Surgery
UCLA Medical Center
Los Angeles

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Horse HAFE?

To the Editor: This letter is stimulated by the recent exchange of views in the journal on high altitude flatus expulsion (HAFE).

During World War II, the US Air Force flew several thousand horses "over the hump" from Burma to China. The horses were flown in C-47's and C-46's, with each flight carrying four horses.

As the planes gained the necessary altitude for the flight the gaseous production in the fuselage of the plane was really impressive. Horses are able to digest cellulose and in doing so there is considerable production of gas. The decreasing atmospheric pressure in the higher altitude would cause a great expansion of the already large intestinal gas volume.

As the planes not only were not pressurized but also not insulated, there was adequate air exchange so there was no chance to learn if the gas production would attain a lethal concentration. However, the odor lingered on in a very impressive fashion.

It would seem fair and proper to designate this example of the entity as a "Lot of Horse HAFE."

O. WILLIAM ANDERSON, MD
Seattle

Editor's note: The expanding volume of comment about HAFE makes it necessary to stem the flow with this letter. Any more discussion could only becloud the issue. This will HAFE to be it.

A Thought for the Year of the Handicapped

To the Editor: With the current attention focused on handicapped persons, can we hope to see the disappearance of such conditions as birth defects? Milunsky in his book *Know Your Genes*?[1] states that there are more than 2,000 identified genetic disorders. How do we proceed in an attempt to decrease the numbers even if we may be unable to eliminate all of them?

Some 30 years ago a slogan was "Let's get the handicapped out of the closets!" The reason for the slogan was that defective infants, especially ones with Down's syndrome, were often not shown to the parents. Instead the parents were told to put him or her in an institution and forget about it. Sometimes the parents were advised to "try again." While I was working with handicapped persons and taking careful family histories myself, it became apparent that the knowledge of a congenital disease in the family was "kept in the closet." Many families to this day are not told about genetic problems until a child with a genetic defect is born. Genetic counseling after the event

is common now, but that obviously is too late in many instances. How can we go about getting people to be open about genetics and such diseases in their family histories? Siblings of a defective child often have said the following to me: "If I marry and have children am I apt to have a child like my brother (sister)? If so I won't have any children. I will adopt one instead."

It should be obvious to everyone working with handicapped persons that there is a very great need for more and better health education in this field. Physicians, other health workers, teachers, parents and children should know their bodies—structure, function, maintenance and reproduction—and they should also "know their genes." Let's be open about it and get the knowledge "out of the closet."

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Blood Pressure Measurement in Children

To the Editor: Having practiced pediatrics and eventually practicing general medicine, for the past 22 years, I have recognized the significance and importance of hypertension in children. The article and editorial on the subject in the April issue were of great value in corroborating the feelings that I have had concerning elevated blood pressures in the pediatric and adolescent age groups.

The description of the method of taking blood pressures in youngsters in this age group, though, leaves something to be desired in the light of some new methodology which has been on the market for the past several years. I am alluding to the technique of taking blood pressure with instruments using oscillofluidics which do not involve the use of a stethoscope and do not need the auscultation of Korotkoff's sounds. These instruments pick up the pulsation of the artery directly through the cuff and through a transducing mechanism, and give you a readout of the patient's blood pressure. I have used the instruments in my private practice and I find that they are fantastically accurate, and particularly useful in the pediatric age group. A crying child, extraneous noises or even a mother trying to soothe the child while you take the blood pressure, will have no effect on the reading of the blood pressure, therefore insuring the accuracy of the reading as compared with the classical type of reading involving use of stethoscopes, microphone amplifiers and the reading of manometers as well as determination of first, second, third, fourth and fifth phases.

The instrument I have used in my office is the Medtek BPI 420, which has been a great boon to me in the taking of blood pressures and might very well foretell the wave of the future in physicians' evaluation of blood pressure in the pediatric age group.

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Eradicating Handgun Violence

To the Editor: I am absolutely appalled by the editorial on violence by handguns in the May issue.[1]

It may well be true that the nation has considerable infatuation with violence by handguns as demonstrated in motion pictures and news media, but how does one conclude that Americans condone violence by handguns? Many, but not all, polls have shown Americans in favor of stricter handgun controls.

Should the medical profession stop its campaign to curb alcoholism? After all, most alcoholics enjoy drinking. Should we stop our efforts to reduce cigarette smoking?

I totally disagree with the contention that banning or registering handguns cannot solve the problem. Obviously it will take many years to reduce the large number of handguns in circulation. The fact that it may take a long time is no argument against making the effort in view of the thousands of people who are killed each year and the many more who are wounded by handguns. It has taken 200 years to eliminate deaths from smallpox. Should we argue that smallpox vaccinations should never have been advocated by the profession in view of the length of time it would take to eradicate this disease?

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Self-Monitoring of Blood Glucose by Diabetic Patients

To the Editor: For decades control of blood glucose in diabetes mellitus has been monitored by testing urine. This semiquantitative method has many limitations but until recently nothing better was available. Among the limitations of urine testing are the following:

- Failure to measure blood glucose in its normal range of 60 to 140 mg per dl because of the renal threshold effect.
- Lack of information about impending hypoglycemia.
- Dependence upon the state of hydration of the patient.
- Inaccuracy when urethral obstruction, kidney disease or pregnancy is present.
- Reluctance of patients to handle urine.
- Broad variation in the blood glucose level for any level of urine glucose.
- Lack of meaning for the patient.

Some of these limitations might be acceptable if the urine glucose correlated with the blood glucose to any extent. The fact is that it does not. Our experience comparing urine test results with simultaneous blood glucose tests as well as numerous published studies[1,2,3] confirm that there is no consistent and reliable connection between urine tests and blood glucose results. Single daily blood glucose tests are no better than urine tests in establishing overall control of blood glucose.

There are now available a number of accurate, inexpensive and acceptable methods by which patients can measure their own blood glucose several times a day.[4-7] All require a finger prick and one drop of blood. Results are determined within one or two minutes. Self-monitoring of blood glucose by patients may be done anywhere and has led to improved diabetic control without increased hypoglycemia. Such control will finally permit us to determine whether long-term complications of diabetes mellitus are a consequence of elevated blood glucose levels.

It is time for physicians to stop using urine test results, for diabetic education courses to stop teaching urine testing to diabetic patients and for patients to learn to test their own blood glucose several times a day.

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Tumorigenic Aspect of Spironolactone

To the Editor: This is in response to the June epitome "A New and Effective Treatment of Hirsutism."[1] The tumorigenic aspect of spironolactone (Aldactone), as recently added to the *Physicians' Desk Reference (PDR)* description of the drug, should not be ignored. Case(s) of cancer in person(s) having used spironolactone have occurred, with the question of degree of relatedness between the drug and the disease yet to be decided.

I know of *one* such case *indirectly*. Dr. Yen and others using the drug should publish both negative and positive reports on tumors in their cases over the long term. The prospect of exchanging hirsutism for tumor is frightening, to say the least.

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Refer to: Rosinski EF, Dagenais F: A comparison of primary care residents with conventional internal medicine and pediatric residents (Medical Education). West J Med 135:245-247, Sep 1981

A Comparison of Primary Care Residents With Conventional Internal Medicine and Pediatric Residents

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A study was done of 15 residency training programs in primary care (not family practice residencies) to determine how the residents compared with their counterparts in conventional programs. Primary care residents are equally or more clinically skilled and equally or better grounded in the science of medicine. Their clinical research is directed toward different issues, and they are decidely more psychosocially oriented.

During the years 1976 through 1980 an intensive study of 15 residency training programs in internal medicine and pediatrics primary care (not family practice programs) in a diverse range of medical schools was conducted. Nine of the residencies were financially supported by the Robert Wood Johnson Foundation, and six were supported by the Department of Health and Human Services. The purpose of the study was to acquire a large amount of descriptive and analytical data on the programs in terms of problems encountered and how they were resolved; goals and objectives; staffing patterns; clinical affiliations; patient population; educational and patient care activities; evaluation; funding, and *institutionalization*—that is, the process by which an educational or patient care activity or program, originally begun on an experimental basis, eventually becomes an established program. According to the study design, a major portion of the study focused on 29 different aspects of the residents themselves. This report deals with only one component, although an important one, of the resident population: how the primary care residents are perceived by faculty, professional staff and peers, training in other, more traditional, residencies sponsored by the same 15 medical schools.

Methods

As part of the study, site visits were made to all 15 programs. While there were several reasons for making the site visits, one of the most compelling was to determine the attitudes of non-primary care residents, faculty and staff toward the 225 residents in primary care internal medicine and pediatrics programs. Because the polled attitudes dealt with personal (and professional) matters, it was thought that some respondents

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might be reluctant to respond to an impersonal questionnaire. However, individual interviews seemed more likely to elicit a more candid response.

The director of each residency training program was contacted and a schedule for the site visit was set up that would include interviews with non-primary care residents, nurses, nurse practitioners, physician assistants, clinic directors, faculty and others who had professional contact with the primary care residents. The program directors were *not* informed as to the purpose or content of the interviews.

An interview plan was prepared and tested before the site visits were made. At the beginning of each interview it was ascertained whether the interviewee had professional contact with the primary care residents in the program, and a determination was made about the extent of the professional interaction and the occasions of the contact. To establish a reference point or criterion group, each person was asked to compare the primary care residents with those in traditional (conventional) internal medicine or pediatrics at the same level of training in the following areas: clinical skills, psychosocial orientation, interest in clinical research and knowledge in the science of medicine. An additional question requested the interviewee to state generally, to the extent possible, how the primary care residents compared as clinicians with those in traditional internal medicine or pediatrics programs. A final question specifically asked, "Other than what we have discussed, do you see the primary care residents as being in any way different from residents in internal medicine (pediatrics)? If so, how are they different?" Interviewees were given an opportunity to respond freely to this last question.

Results

In all, 290 people were interviewed. Interviewees included departmental chairmen, full professors, associate professors, assistant professors, instructors, and professional or supporting staff such as nurses, nursing supervisors, clinic directors and social workers, as arranged by the program directors. The responses to the first four questions are recorded in Table 1.

About 70 percent (n = 280) of the respondents perceived the primary care residents as having clinical skills that were equal to those of the traditional residents. Roughly 12 percent perceived the primary care residents as being either less or more clinically skilled, whereas about 6 percent would not make a response. The bulk of those who said "can't say" were allied health personnel who felt it would be presumptuous to make a statement.

TABLE 1.—*How Four Qualities of Primary Care Residents Are Perceived by Professional Staffs*

Professional Qualities	*Less (percent)*	*Equal (percent)*	*More (percent)*	*Can't Say (percent)*	*N**
Clinical skills	12	71	11	6	280
Psychosocial orientation	2	28	66	5	289
Interest in clinical research	26	47	5	22	285
Knowledge of the science of medicine	12	68	4	17	273

*Number of respondents who provided usable answers.

TABLE 2.—*How Primary Care Residents Are Perceived as Clinicians*

How Perceived	*N**	*Percent*
Not as good	28	10
Equal	182	64
Better	42	15
Can't say	33	12

*Number of respondents who provided usable answers.

Another question was "Are the primary care residents less, equally, or more psychosocially oriented?" The primary care residents were perceived as more psychosocially oriented by 66 percent of the respondents, as equally psychosocially oriented by 28 percent of the respondents and as less psychosocially oriented by only 2 percent of the respondents.

For interviewee perception of whether the primary care residents had more, the same or less interest in clinical research, 47 percent of those answering perceived the primary care residents as equally, 26 percent as less, and only 5 percent as more interested in clinical research. However, while responding to this question, most interviewees volunteered to say that the primary care residents' research interests were geared more toward "health care delivery." The "can't say" percentage (22 percent) was so high because the nurses and allied health personnel indicated, quite frankly, during the interviews that they were not competent to judge the residents on these matters.

Finally, two thirds (68 percent) of the respondents perceived the primary care residents as being equally as knowledgeable as traditional residents in the science of medicine, 12 percent as less knowledgeable and only 4 percent as more knowl-

edgeable. The 17 percent "can't say" response is probably due to the same reluctance of nurses and allied health personnel to make a judgment.

The responses to the question "To the extent that one can generalize, as clinicians, how do you compare the primary care residents with those in [a traditional residency]" are reported in Table 2. Of those interviewed 79 percent perceived the primary care residents as being either equal or better clinicians than the other residents (Table 2).

A final question in the interview asked whether the respondent saw the primary care residents as "being different" from the more traditional ones. About 80 percent viewed them as being different and provided comments on what they saw as the differences. It would be difficult to cite here all the comments made. However, the following are typical responses: "They are willing to work as a team." "They are better prepared to begin office practice." "They are different in ideology, attitude, and responsiveness to broader issues." "The primary care residents tend to have broader interests and breadth of outreach." "They have a wider variety of skills—medical, social, community, etc." And finally, a typical response that seems to summarize the differences, "Primary care residents are more interested in people."

Discussion

Academic institutions, especially university medical centers, are not known for their enthusiam to initiate new approaches to the delivery of health services by modifying either their educational programs or how they provide university-based medical services. This observation was confirmed by the reluctance of many medical administrators and university physician-educators in the early 1970's to support with enthusiasm the development of residency training programs in primary care. While this reluctance could be illustrated by any number of anecdotes, most often critics of primary care either verbally or through implied behavior—although never publicly—transmitted the message that primary care residents were "not as good" as residents in traditional residencies of medicine and pediatrics. The "not as good" opinion was reflected in how the primary care residents were perceived in terms of their clinical skills, scientific background and research interest.

This study should lay to rest this unwarranted stereotype of residents in primary care medicine and pediatrics programs. Most of the people interviewed in this study had no vested interest in the success or failure of the programs, and, indeed, many of them were hostile to them when they were begun at their institutions. That such large numbers now saw the primary care residents as equally or more skilled (82 percent), and equally or more knowledgeable in the science of medicine (72 percent), is a testimonial to the quality of the residents and the quality of the training programs. Furthermore, that 79 percent of those interviewed summed up their impression of the primary care residents as being equal or better clinicians than their counterparts in traditional internal medicine and pediatrics should allay some of the arguments of critics of primary care physicians.

What should not be surprising is that such a large number (66 percent) of respondents perceived the primary care residents as being more psychosocially oriented. With the primary care residencies geared more "toward the community," it seems logical that the more psychosocially oriented medical students will be attracted to the programs and have that orientation reinforced. And that is as it should be, for if there is to be one salient characteristic that distinguishes the primary care residents from their colleagues in internal medicine and pediatrics it should be their psychosocial orientation toward health and patient care.

Refer to: Crain LS, Dienst ER, Malloy MJ: The effects of primary care versus traditional training on career choice in pediatrics (Medical Education). West J Med 135:248-251, Sep 1981

The Effects of Primary Care Versus Traditional Training on Career Choice in Pediatrics

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In response to concerns questioning the relevance for future pediatric generalists of traditional hospital-based, subspecialty-oriented pediatric residency training, new residency programs emphasizing increased ambulatory, continuity care training experiences have been developed.

We compared the career activities of physicians who had received their pediatric residency training in the traditional, predominantly inpatient program and in the predominantly ambulatory primary care program at the University of California, San Francisco. Three groups were surveyed: (1) pre-1975, *those who received training in the traditional program before 1975, (2)* post-1975, *those who were trained in the traditional program after 1975 and (3)* primary care, *those who received their training in the primary care program beginning in 1975.*

The results indicate that more than twice as many former primary care residents as traditional residents are practicing primary care. Since the development of two pediatric training tracks, *satisfaction with program relevance has increased among those who practice primary care. The results indicate that there is a greater commitment to primary care practice among residents trained in the primary care program.*

CONCERN FOR THE TREND toward increasing specialization had led during the past decade to a number of developments designed to increase the number of well-trained primary care physicians. In 1976 the Health Professions Educational Assistance Act (PL 94-484) was passed to increase the number of residency positions available in "primary care" fields: medicine, pediatrics and family practice.[1] In addition, private and federal support became available for the development of new residency training programs specifically oriented to primary care. It was recognized that

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TABLE 1.—*Current and Planned Primary Care Career Activities by Program Group*

	Current Career						*Future Career*					
	Traditional						*Traditional*					
	Pre-1975		*Post-1975*		*Primary Care*		*Pre-1975*		*Post-1975*		*Primary Care*	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Primary care only	22	(26)	6	(21)	8	(62)	22	(27)	6	(21)	6	(55)
Primary care and other ..	16	(19)	5	(18)	1	(8)	14	(17)	1	(4)	4	(36)
No primary care	45	(55)	17	(61)	4	(30)	47	(56)	21	(75)	1	(9)
TOTALS	83	(100)	28	(100)	13	(100)	83	(100)	28	(100)	11*	(100)

*Two respondents failed to answer.

traditional hospital-based residency training programs in pediatrics and medicine do not necessarily encourage or sustain a career commitment to primary care. Indeed, a significant proportion of the residents in traditional medicine programs who enter with intent to practice general medicine shift to subspecialty careers.[2] In medicine, this pattern of career goal shift has resulted in relatively few university-trained internists practicing general medicine.[3,4] A recent study comparing the career choice patterns of residents in a traditional internal medicine program with those in a new primary care-oriented program suggests that innovations in residency training directed at primary care may succeed in maintaining resident interest in primary care.[5]

Although most nonacademic pediatricians are practicing general pediatrics,[6] concern has been expressed that traditional residency training in pediatrics does not meet the needs of generalists, and greater training emphasis should be placed on ambulatory, continuity experiences.[7] A recent study of career satisfaction and change among practicing pediatricians showed that 21 percent had already made modifications toward increasing subspecialization and many more, especially the younger physicians, were contemplating changes toward subspecialization.[8]

The present study was designed to compare the career activities of physicians who had received their residency training in the traditional and primary care *tracks* of the pediatrics residency program at the University of California, San Francisco (UCSF). The study focused on the primary care versus subspecialization practice orientations of graduates of both tracks beginning in 1975. Those who had been trained in the traditional UCSF pediatrics program between 1970 and 1974, before the primary care track was initiated, were also surveyed. The study was part of a larger project to evaluate the primary care residency training program.

Program Description

In 1975 the Division of Ambulatory and Community Medicine, in collaboration with the Departments of Internal Medicine and Pediatrics, began residency training programs in primary care pediatrics and in primary care internal medicine.

In addition to traditional training in hospital inpatient services, the primary care program emphasizes training in ambulatory care, with a multispecialty primary care clinic (MSPCC) as the clinical base. The MSPCC emphasizes continuity of care with residents assuming primary responsibility for a panel of patients throughout the three years of training. A family orientation and team approach to care are stressed. Other features that distinguish the primary care pediatrics program from a traditional residency include significantly more time spent in the ambulatory setting, outpatient subspecialty clinic rotations, more general inpatient experiences and an emphasis on behavioral science training throughout the three years.

Method

To compare the current career activities and future career plans of former residents in the pediatric traditional and primary care tracks, a brief questionnaire was mailed to 156 former residents who had received their training at UCSF beginning in 1970; 125 (79 percent) responses were received.

The respondents were separated into three groups: (1) *pre-1975,* those who entered their residency training at UCSF before 1975, (2) *post-1975,* those who entered the traditional pediatric

TABLE 2.—*Mean Ratings of Relevance of Training By Current Career Activity**

Current Practice	Traditional Pre-1975	Traditional Post-1975	Primary Care	Analysis of Variants F	Analysis of Variants P
Primary care only	3.6	4.5	4.5	4.46	0.02
Primary care and other	4.0	3.8	4.0	0.09	0.91
No primary care	4.1	3.9	3.5	4.86	0.004

*Scale: 5.0 = very relevant; 1.0 = very irrelevant.

residency program in 1975 or thereafter, and (3) *primary care,* those who received their training in the primary care program beginning in 1975.

Results

Table 1 shows a comparison of the current career activities and future plans of former residents in the three program groups. Whereas 62 percent of those in the primary care program are engaged exclusively in a primary care practice, only 26 percent and 21 percent of those in the pre-1975 and post-1975 traditional program groups are exclusively in primary care. Twice as many former residents from the traditional program as from the primary care program are engaged in career activities that entirely exclude primary care.

We recognized that current career activities (especially for recent graduates) might be temporary. A question regarding future career plans enabled us to assess expected long-range career orientations. The findings with regard to exclusive primary care practice are quite similar to the findings for current career activity, with twice as many primary care residents as traditional residents indicating intent to practice primary care exclusively. Of the primary care residents, 91 percent expected to practice primary care in the future, whereas only 44 percent and 25 percent, respectively, of the pre-1975 and post-1975 traditional program residents mentioned primary care as a planned component of their future practices. This suggests a considerably stronger long-term commitment to primary care practice among those who received their training in the primary care track.

Although the current and future career orientations of those who received special training in primary care are clearly more strongly oriented to general pediatric practice, a significant proportion of those who received traditional training are engaged in the practice of primary care (about 40 percent). In fact, more than 20 percent of the traditionally trained residents are engaged exclusively in primary care practice. How do these traditionally trained primary care pediatricians view the adequacy of their training for their current career practices? Are general pediatricians who received special primary care training more satisfied with their training? Table 2 presents the mean evaluation ratings on a 5-point Likert-type scale for each of our three program groups and compares the ratings of those engaged in primary care with those not practicing primary care. An analysis of variance (ANOVA) was conducted comparing the mean ratings of program groups, while controlling for practice orientation. The results suggest that among the pediatricians who practice primary care exclusively, those who trained in the traditional program before 1975 were the least satisfied with the relevance of their training. For those receiving training after 1975, there is very little difference in the ratings of those in the traditional and primary care pathways.

Discussion

The results of this study show that there is a stronger current and long-term commitment to primary care practice among those who participated in the primary care program than among those who received traditional hospital-based pediatric training. Although the traditional program continues to be hospital-based and most of its graduates continue to eschew primary care practice, a number of program modifications have been attempted since 1975, partly in response to the needs of those traditional program residents who will practice at least some primary care. These modifications, including a continuity clinic experience and increased elective time, may have contributed to the increased satisfaction expressed by primary care practitioners who were trained after 1975 in the traditional program.

The availability of a choice between primary care and traditional training since 1975 has provided residents an opportunity to select the track most compatible with their training and career goals. A previous study of the training goals of residents in the two tracks indicated that those in the traditional program had a stronger orientation to hospital-based training.[10] The results of the present study further confirm the implications of

these differences in goal orientation for actual career practice and provide evidence that a university-based primary care training program can contribute to providing increased numbers of well-trained pediatricians committed to primary care pediatrics practice.

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Refer to: Herbert V: Nutrition cultism (Informed Opinion). West J Med 135:252-256, Sep 1981

Nutrition Cultism

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IN HIS ARTICLE "Historical Aspects of Food Cultism and Nutrition Quackery," a section of the book *Food Cultism and Nutrition Quackery*,[1] Emory University historian James Harvey Young pointed out that religion has influenced food choice from the earliest days of primitive medicine. Foods have been used through the ages as offerings to the gods to soothe their anger or win their gratitude. Ceremonies involving food exist in all major religions. In *Food: Facts, Foibles, and Fables, The Origins of Human Nutrition*,[2] Simeons stated, "I know from personal experience that it is not uncommon for an orthodox Hindu to prefer dying of pernicious anemia to taking liver extract" (which would be curative). In his book *Cornflake Crusade*,[3] Carson noted that the first name given to the processed dry cereal that eventually became cornflakes was "Elijah's Manna," thus invoking the power of religion and magic in the service of food cultism.

It is unfortunately true in the United States that there is no law against misinforming about nutrition provided one does not do so on the label of a product. Hence the proliferation of radio and television "nutritionists" and fast-buck physicians and PhD's on talk shows, who make millions from their books, articles and public appearances promoting sensational nutrition panaceas for all the ills of humankind.

Sensationalism and scare tactics are the hallmarks of all demagoguery. This is as true for the demagoguery that creates nutrition cults as it is for the demagoguery that creates other cults.

The basic scientific axiom that no alleged nutrient is safe until proved to be safe or efficacious until proved to be efficacious can be said to have been enunciated when God told Adam not to eat that apple—and the first demagogue of nutrition cultism can be said to have been Satan, when he told Eve to go ahead and have Adam eat the apple. So it has been ever since, with one demagogue after another doing good for himself and harm to others by promoting one after another dangerous remedy as safe, and one after another worthless remedy as preventive or therapeutic, or both.

Most of the "nutrition" advice given to the public in newspapers, magazines, radio, television and popular books ranges from deceptive and misleading to downright fraudulent. The media introduce as "nutrition experts" a number of popular figures whose only nutrition credentials may be criminal convictions for nutrition fraud, coupled with the charisma and amorality which allow them to make sensational claims and use the scare tactics that enchant the public, to sell newspapers, magazines, air time and products.

Nutrition is a science; it is not a religion. Those who ask, "What do you believe about this or that nutrition claim?" and those who state they *believe* this or that about nutrition are talking religion and not science. What nutrients can and cannot do in the human body is determined by the chemical structure of the nutrient and the specific biochemical reactions in the human body in which the chemical structure is capable of becoming involved. Nutrition science is largely a branch of biochemistry. Many of the happy fictions of nutrition cultism are flatly contrary to the scientific facts about what the given nutrient or food substance is capable of doing in human biochemistry.

Nutrition cultism has cleverly profited from dis-

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torting the decision by millions of Americans to assume greater control over their own fate into a cry to abandon science and dependency on scientists, and prove their "independence," "personal responsibility" and "freedom of choice" by making decisions based on anecdote, fraud and misrepresentations rather than making informed judgments.

We need to teach young people to ask "How do we know the things that we know?" The fundamental sciences of logic and epistemology teach how to evaluate the validity of statements. These sciences should be basic teaching in our schools, but are not. We need to teach how belief can be rationally established.

In the realm of science, we know things because they prove to be so when subjected to testing. In science, claims are considered untrue until proved true in studies that separate cause and effect from coincidence. The double-blind controlled trial is a classic such scientific study.

A word should be said about the penchant of the media to promote "debates" between responsible nutrition scientists and promoters of nutrition quackery, for the purpose of sensationalism but disguised as giving a fair hearing to both sides. Is it "giving a fair hearing to both sides" to invite a rapist to provide his side of the story—that is, why rape is good? If not, then why is it appropriate to invite a rapist of the mind—a promoter of health quackery—to present his deceptions, distortions and misrepresentations as if they were fact? When a scientist points out these are lies, the lay audience, without the scientific background or time to delve into the scientific literature to ascertain who is telling the truth, simply concludes that there is just a difference of opinion between two scientific equals (otherwise why would the talk-show host put the quack on?).

In medical school we learned that anecdotes and testimonials are worthless as evidence of either safety or efficacy of a claimed remedy. We learned that before accepting as valid a claim of cure, it is first necessary to ascertain that the patient had the disease, that the diagnosis was established by objective criteria and that the claimed cure resulted *from* the therapy rather than merely being coincidental *with* the therapy. We learned that 80 percent of all symptoms with which patients present disappear with no therapy, so that quacks produce "cures" in four out of five cases, and the distinction between the quack and the genuine physician is that the physician is able to correctly diagnose and treat that one in five who has not had a spontaneous "cure."

We learned in medical school that most chronic diseases progress in halts (remissions) and starts (exacerbations) rather than inexorably, and sometimes there are permanent remissions with no therapy. It is easy to mistake a remission occurring in the natural history of the disease for a therapeutic triumph due to an irrelevant "therapy." That is why adequate numbers of untreated patients (controls) must be compared with adequate numbers of treated patients before accepting a therapy claim, such as the megadose vitamin C self-cure for collagen disease recited by Norman Cousins in his best-seller *Anatomy of an Illness*.[4] As reviewer Terence Smith pointed out, "On one hand, Cousins' criticisms of nutrition practices in the United States read like passages from *Prevention* magazine—emotionally appealing but scientific nonsense. On the other hand, many of his thoughts on our American approach to sickness and health are right on the mark."[5]

Unfortunately, the farther away we get from medical school, the more likely we are to forget those hard lessons, and accept as valid the nutrition miracles promoted by the media, who present anecdotes, testimonials and undocumented conclusions as fact, as if such irresponsible promotion was responsible scientific evidence. The willingness of the media to promote nutrition cultism as long as it is sensational is compounded by the unwillingness of most scientific journals to publish facts that could arouse the ire of cultists and promoters.

Emory University Professor of History James Harvey Young has distilled from his decades of study a ten-point profile of health cultism and quackery:[6]

(1) Exploitation of fear.

(2) Promise of painless treatment and good results.

(3) Claims of a miraculous scientific breakthrough.

(4) Simpleton science: Disease has but one cause, and one treatment is all that is needed to fight it. (Bad nutrition causes all disease; good nutrition cures it.)

(5) The Galileo ploy. (Like Galileo, we cult gurus are misunderstood by blind scientists, but are destined to be heroes to future generations.)

(6) The conspiracy theory (also known as "the establishment is out to get us").

(7) The moving target: Shifts in theory to adjust to circumstances. Laetrile went from drug to "vitamin," from cure to palliative to preventive, from low to high dosages, from working alone to never working alone, from one chemical formula to another, and so forth. "B_{15}" ("pangamate") is any chemical or combination of chemicals the seller chooses to put in the bottle.

(8) Reliance on testimonials.

(9) Distortion of the idea of "freedom": By distorting "freedom of *informed* choice" to "freedom of choice," snake-oil salesmen acquire freedom to defraud, and their victims can lose their money, their health and their lives.

(10) Large sums of money are involved: Nutrition cultism is a multi-billion dollar industry. Laetrile was a billion-dollar-a-year industry for the product alone in the United States as of June 1979. "B_{15}" ("pangamate") was the largest selling "health food" in the United States in 1978, according to the *Wall Street Journal,* even though it is a label and not a product, and each manufacturer tosses any chemicals he chooses into bottles so labeled.

Young[6] summarized the success of Laetrile as "fear of cancer, suspicion of government, a primitivistic retreat from complex civilization to 'natural' ways, skillful organization, adept lobbying, and a shrewdness at borrowing time-tested techniques from quackery's well-stocked past."

The State of California panders to nutrition cultism by allowing the creation of scientifically worthless mail-order doctorates in nutrition. Such doctorates may be given by any businessperson who secures approval from California to be "authorized" to be a university. The only requirements imposed by California before "authorizing" a university are that it must have a curriculum and faculty (no quality criteria for either are required), have $50,000 of net assets in California (which can be the home or office of the businessperson) and file with the State of California an annual affidavit of "full disclosure." California forbids its mail-order doctorate-granting universities to represent themselves as either "approved" or "accredited," which are the two levels above "authorized" in the California descriptive lexicon of university quality, but not one person in a thousand is aware of this fact, nor does California require businesspersons who send out literature advertising mail-order PhD's in nutrition to state this fact. (The latest in misleading claims by California's "diploma mills," which are "authorized" by California, is "accreditation" by "accreditation mills," —that is, independent accrediting agencies not recognized by either the United States Office of Education or the California Department of Education.) California law should, but does not, require "authorized" institutions to prominently publicize in all their literature that they are not approved or accredited and

> Filing pursuant to this subdivision shall not be interpreted to mean, and it shall be unlawful for, any [authorized] institution to expressly or impliedly represent by any means whatsoever, that the State of California, Superintendent of Public Instruction, the State Board of Education or the Department of Education, has made any evaluation, recognition, accreditation, approval, or endorsement of the course of study or degree.[7]

Persons with unapproved or unaccredited degrees in nutrition must be considered as having no educational qualifications that would make them experts in the science of nutrition until proved otherwise.[8] A report by the National News Council on a California "nutrition university," which had been falsely represented in a national magazine as "the real thing," appears in the March-April 1981 issue of the *Columbia Journalism Review.*[9]

To understand why nutrition quackery and cultism flourish, *cherchez le dollar.* It is necessary to recognize that nutrition cultism is big business, based on exploitation, deception, misrepresentation, anecdote and testimonial. Physicians should be aware that fundamental to the success of this business is the group defamation of physicians and other health scientists. By destroying their credibility, the snake-oil purveyor can then say, "You can't trust the establishment; trust me!" It is also fundamental to the success of nutrition cultism that the public accept as valid the reversals of the two basic scientific canons that no therapy is safe until proved safe or effective until proved effective. The reversals read, "safe until proved unsafe, and effective until proved ineffective." More than 50 people died in connection with self-administered protein-sparing modified fasts before the media and the public realized that calling something nutritional therapy does not allow reversing the basic canons of therapy; that lesson was quickly lost on them.

The power of the promoters of nutrition cultism is delineated in the chapter "Laetrile: The political success of a scientific failure" in the 1980 book *Health Quackery.*[10] As that article notes,

the proponents of Laetrile are . . . increasingly turning to legislators who seem susceptible to the pressure group tactics used by the pro-Laetrile lobby . . . the government's ability to rid the marketplace of quack remedies of all kinds may be jeopardized. . . .

The power of political pressure is being felt even in the scientific world. Generally, major cancer research centers consider it unethical to test a drug on human beings unless it first shows promise in animals. Laetrile has shown no such promise. Nevertheless, the National Cancer Institute and the Memorial Sloan-Kettering Cancer Center—two organizations that have conducted extensive animal tests on Laetrile and found it ineffective—say that controlled human tests of Laetrile may now be necessary.

"Laetrile is a highly emotional issue that will not soon go away," an NCI official explained. "By conducting very careful human tests, we hope to prove once and for all time that the stuff is useless, and doesn't do anything that it's touted for."

The well-meaning National Cancer Institute trial has lent a specious legitimacy to Laetrile. Laetrile is 6 percent cyanide by weight, and can kill when given by mouth or rectum, since the cyanide is released by the plant enzyme β-glucosidase present in many nuts, fruits and vegetables eaten with Laetrile, and also present in colon bacteria. Laetrile seized by the FDA contains 0 to 80 percent of label strength, and this explains the relatively low toxicity of the Laetrile industry product. The National Cancer Institute Laetrile trial is being done in a fashion to avoid acute poisoning. Only 0.5-gram doses of Laetrile, given orally, are used, and then there is a one-hour wait to allow the Laetrile to clear from the stomach before any plant food, which might release cyanide from the Laetrile, is fed. Even with this precaution, acute toxicity occurred in a patient given an ounce of almonds one hour after each Laetrile dose, diarrhea occurred in another, and the remaining four in the Mayo Clinic toxicity trial had blood and urine cyanide and thiocyanate levels consistent with low-grade chronic cyanide toxicity. The minimum lethal dose of cyanide is 50 to 60 mg; 1 gram of pure Laetrile contains 60 mg of cyanide. Given parenterally, Laetrile just creates expensive urine. As repeatedly pointed out, most recently by Koeffler and co-workers,[11] Laetrile is chemotherapy, but is worthless chemotherapy because the dose that kills the cancer kills the patient (that is, it has a host to tumor therapeutic ratio of 1:1, which is unacceptable). Acceptable chemotherapy must have a therapeutic ratio such that the dose that kills the tumor is less than the dose that kills the patient. Because promoters of quackery empty words of their dictionary meaning in their skillful use of specious logic, they ignore the fact that Laetrile is a chemical, refer to Laetrile as "nontoxic therapy," and contrast it to chemotherapy.

We are now witnessing the nutrition cultism of another program—this one having achieved wide public acceptance of an unpalatable low calorie diet, only 10 percent of whose calories are derived from fat. There are no data in the scientific literature to show that the program in question results in reduced rather than increased morbidity and mortality as compared with equivalent low calorie diets with higher percentages of calories derived from fat. The current average American diet derives 42 percent of its calories from fat. Moderation and variety are the keys to good nutrition: a 10 percent fat diet is not moderation and reduces variety, since it requires sharp reduction in intake from two (meat and milk) of the four (meat, milk, grain, fruit and vegetable) basic food groups. A fifth food group (fats, alcohol and sugar) has recently been added by Canadian and American federal agencies, in part to assure supply of the essential fatty acids arachidonic and linoleic, and in part to enhance palatability.

In an effort to bring together for the public and health professionals the facts as they relate to some of today's most prevalent nutrition cults, including all the above information, and all the pertinent scientific references, a number of articles recently published in the scientific literature were updated to 1980 and brought together in the book *Nutrition Cultism*.[12] The book is divided into three parts: nutrition cultism, ethical medicine and nutrition facts. Among the subjects covered in Part I are cyanide poisoning from Laetrile, mutagenesis produced by "B_{15}," destructive effects of "nutritional and metabolic antineoplastic diets," and hot fictions versus cold facts of megavitamin therapy and the vitamin craze.

Among the subjects covered in Part III are the definitions of a vitamin, nutritional assessment with respect to water-soluble vitamins, the 1979 American Medical Association "Concepts of Nutrition and Health,"[13] and the 1980 National Academy of Sciences publication *Toward Healthful Diets*,[14] with commentary pro and con relating to whether or not healthy Americans should cut down on dietary cholesterol.

A closing thought: Epidemiologic studies reviewed in many places, including *Toward Healthful Diets*,[14] show that a high level of cholesterol in serum is a risk factor for coronary artery disease. Prospective epidemiologic studies show a low

serum level of cholesterol is associated with an increased risk of cancer.[15-17] Are either or both of these epidemiologic observations effect rather than cause? Partly each? Effect in some, cause in others? Epidemiology teaches coincidence; it does not teach cause. Intervention trials teach cause. Should we abandon the scientific method of determining whether an association is cause-and-effect or coincidence and insist every American jump on the low cholesterol bandwagon? Is it not wiser to limit the recommendation of a low-cholesterol diet to those whose serum lipids have been measured, and for whom a medical judgment was made that a low cholesterol diet is in order, based on adequate evaluation of the clinical and laboratory data?

An interesting fact is that a number of authors of popular nutrition books may have a diploma-mill* PhD in nutrition,[18] a PhD in a field other than nutrition, or an MD degree with the right to practice limited or revoked by their home state, and sometimes also a criminal conviction in connection with some of their "nutrition" activities. To find out if this is the case for an author whose writings appear questionable to you, you can consult *Nutrition Cultism*[12] or *The Health Robbers,*[19] or you can write to the Food and Drug Administration, Litigation and Recall Staff, 5600 Fishers Lane, Rockville, MD 20857, or your state's health department.

*"Diploma mill" is defined in the *Random House Dictionary of the English Language* as "a pretended institution of higher learning existing for profit only and granting degrees without demanding proper qualifications of the recipients."

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NUTRITION—Volume 1—William J. Darby, Nutrition Foundation, Editor; Harry P. Broquist and Robert E. Olson, St. Louis University, Associate Editors. Annual Reviews Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1981. 510 pages, $20.00 (USA), $21.00 (elsewhere).

CARDIOLOGY: 1981—Edited by William C. Roberts, MD; Dean T. Mason, MD; Mary Allen Engle, MD, and Lawrence H. Cohn, MD. Yorke Medical Books, 666 Fifth Avenue, New York, NY (10019). 1981, 364 pages, $39.50.

CAUTION: 'KINDNESS' CAN BE DANGEROUS TO THE ALCOHOLIC—Abraham J. Twerski, MD, Medical Director, Gateway Rehabilitation Center, and Clinical Director, Department of Psychiatry, St. Francis General Hospital, Pittsburgh; ordained Rabbi, and Assistant Professor of Psychiatry, University of Pittsburgh School of Medicine. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1981. 172 pages, $9.95 (hard cover), $4.95 (paperback).

THE CHANGING YEARS—The Menopause Without Fear—Third Revised Edition—Madeline Gray. Doubleday & Company, Inc., 245 Park Avenue, New York, NY (10017), 1981. 277 pages, $13.95.

CLINICAL ARTHROGRAPHY—Rolf D. Arndt, MD, Radiologist, St. John's Hospital and Health Center, Santa Monica, Assistant Clinical Professor of Radiology, University of California, Los Angeles; John W. Horns, MD, Radiologist, St. John's Hospital and Health Center, Santa Monica, Assistant Clinical Professor of Radiology, University of California, Los Angeles; Richard H. Gold, MD, Professor of Radiology, Chief of Skeletal Radiology, University of California, Los Angeles; with a special contribution on temporomandibular joint arthrography by Donald D. Blaschke, DDS, Assistant Professor, Section of Oral Radiology, University of California, Los Angeles, School of Dentistry. Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1981. 212 pages, $30.00.

THE COMPLETE NEW GUIDE TO PREPARING BABY FOODS—Sue Castle. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1981. 336 pages, $13.95.

CORE PATHOLOGY: Fundamental Concepts and Principles—Chandler Smith, MD, Professor and Chairman, Department of Pathology, University of Missouri-Kansas City School of Medicine. Medical Economics Books, Box 157, Florence, KY (41042), 1981. 472 pages, illustrated, $39.50.

CURRENT SURGICAL DIAGNOSIS & TREATMENT—5th Edition—Edited by J. Englebert Dunphy, MD, Professor of Surgery Emeritus, University of California, San Francisco; and Lawrence W. Way, MD, Professor of Surgery, University of California, San Francisco, Chief of Surgical Service, Veterans Administration Medical Center, San Francisco; and associate authors. Lange Medical Publications, Drawer L., Los Altos, CA (94022), 1981. 1,138 pages, $25.00.

EATING AND ALLERGY—Robert Eagle. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1981. 201 pages, $11.95.

INFERTILITY: A PRACTICAL GUIDE FOR THE PHYSICIAN—Edited by Mary G. Hammond, MD, and Luther M. Talbert, MD, Division of Reproductive Endocrinology and Fertility, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine. Health Sciences Consortium, 200 Eastowne Drive, Suite 213, Chapel Hill, NC (27514), 1981. 134 pages, $14.95, plus $1.00 for postage and handling (softbound).

THE INVISIBLE ADDITIVES—Environmental Contaminants in Our Food—Linda R. Pim. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1981. 269 pages, $17.95 (hardbound), $9.95 (paperback).

MAINTENANCE HEMODIALYSIS—Lucius F. Wright, MD, Major, Medical Corps, United States Army; Chief, Nephrology Service, Department of Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 225 pages, $28.50.

MANUAL FOR EYE EXAMINATION AND DIAGNOSIS—Second Edition—Mark W. Leitman, MD, Attending, Middlesex General Hospital and St. Peter's Medical Center, New Brunswick, NJ; Samuel Gartner, MD, Clinical Professor, and Paul Henkind, MD, PhD, Professor and Chairman, Department of Ophthalmology, Albert Einstein College of Medicine, Montefiore Hospital and Medical Center, The Bronx, NY. Medical Economics Books, Box 157, Florence, KY (41042), 1981. 75 pages, $8.95.

A MIRACLE TO BELIEVE IN—Barry Neil Kaufman—Doubleday & Company, Inc., 245 Park Avenue, New York City (10019), 1981. 313 pages, $12.95.

NEW LEADS IN CANCER THERAPEUTICS—Edited by Enrico Mihich, MD, Director, Department of Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, New York. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 162 pages, $27.50.

NUTRITION AND MEDICAL PRACTICE—Edited by Lewis A. Barness, MD, Professor & Chairman, Department of Pediatrics, University of South Florida College of Medicine; with Yank D. Coble, Jr., MD, Specialist in Endocrinology & Nutrition, Jacksonville, FL; Donald I. MacDonald, MD, Pediatrician, Clearwater, FL; and George Christakis, MD, MPH, Chief, Nutrition Div., Dept of Epidemiology & Public Health, University of Miami School of Medicine. AVI Publishing Company, Inc., P.O. Box 831, Westport, CT (06881), 1981. 408 pages, $17.00, U.S. & Can; other countries, $19.50.

NUTRITIONAL ANALYSIS SYSTEM—Debra Lynn Dadd, Robert C. Dadd, Joseph J. McGovern, Jr., MD. Nutritional Research Publishing, 1737 Union Street, San Francisco (94123), 1980. 138 pages, $12.95.

OBSTETRIC ULTRASOUND: APPLICATIONS AND PRINCIPLES—Edited by W. S. Van Bergen, MD, Clinical Assistant Professor of Obstetrics and Gynecology, Southern Illinois University School of Medicine, Springfield, Illinois. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 157 pages, $19.95.

THE PARENT'S WHEN-NOT-TO-WORRY BOOK—Barry B. Behrstock, MD, Assistant Clinical Professor of Pediatrics, University of California, Irvine, Staff Physician, Children's Hospital of Orange County; with Richard Trubo, a member of the American Medical Writers Association. Harper & Row, Publishers, 10 East 53rd Street, New York City (10022), 1981. 262 pages, $11.95.

PEDIATRIC AND ADOLESCENT GYNECOLOGY CASE STUDIES—Richard R. Brookman, MD, Associate Professor of Pediatrics, Director, Adolescent Medicine, Department of Pediatrics, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia. Medical Examination Publishing Co., Inc., 969 Stewart Ave., Garden City, NY (11530), 1981. 573 pages, $20.00 (paperback).

PREVENTIVE AND COMMUNITY MEDICINE—Second Edition—Edited by Duncan W. Clark, MD, Professor of Preventive Medical and Community Health, Downstate Medical Center, State University of New York, Brooklyn; and Brian MacMahon, MD, PhD, DPH, Professor and Head, Department of Epidemiology, Harvard School of Public Health, Boston. Little, Brown and Company, 34 Beacon St., Boston (02106), 1981. 794 pages, $24.95.

PREVENTIVE HEALTH CARE—Edited by R. S. Chang, MD, DSc, Professor of Medical Microbiology and Family Practice, University of California, Davis, School of Medicine; Medical Director, Davis Free Clinic. G. K. Hall & Co., 70 Lincoln Street, Boston (02111), 1981. 492 pages, $28.00.

PROFILE OF THE RESIDENCY TRAINED FAMILY PHYSICIAN IN THE UNITED STATES 1970-1979—Editor: John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington School of Medicine, Seattle. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1981. 68 pages, $12.00 (paperback).

PROTOCOLS FOR PREHOSPITAL EMERGENCY MEDICAL CARE—Jean Abbott, MD, Emergency Physician, Boulder Community Hospital, Boulder, Colorado; Marilyn Gifford, MD, Emergency Physician, EMS Coordinator, St. Joseph's Hospital, Denver; Clark Chipman, MD, Chief, Emergency Services, Emmanuel Hospital, Portland, Oregon; Joseph Engelken, MAPA, Program Director, Emergency Medical Training, School of Allied Health, University of Kansas Medical Center, Kansas City; and Peter Rosen, MD, Director, Division of Emergency Medicine, Denver General Hospital, Clinical Professor of Emergency Medicine, University of Oregon. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1980. 191 pages, $11.95 (softbound).

PULMONARY PHYSIOLOGY IN CLINICAL MEDICINE—Gennaro M. Tisi. MD, Associate Professor of Medicine, University of California, San Diego, School of Medicine, Chief, Pulmonary Section, San Diego Veterans Administration Hospital. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, MD (21202), 1980. 282 pages, $25.00.

RADIOLOGY OF THE PEDIATRIC ELBOW—Armand E. Brodeur, Michael J. Silberstein and E. Richard Graviss. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 234 pages, $39.95.

REVIEW OF MEDICAL PHYSIOLOGY—10th Edition—William F. Ganong, MD, Professor and Chairman, Department of Physiology, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 628 pages, $17.00.

RIGHTS AND RESPONSIBILITIES IN MODERN MEDICINE—Proceedings of the 1979-1980 Conferences on Ethics, Humanism, and Medicine at the University of Michigan, Ann Arbor—Editor: Marc D. Basson, fourth year medical student, University of Michigan—Volume 50 in Progress in Clinical and Biological Research. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1981. 254 pages, $22.00.

SEROLOGY AND IMMUNOLOGY—A Clinical Approach—William D. Stansfield, California Polytechnic State University. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1981. 388 pages.

TOPICAL STEROID TREATMENT FOR ASTHMA AND RHINITIS—Edited by N. Mygind, MD, Senior Lecturer in Otopathology, Rigshospitalet, Copenhagen; and T. J. H. Clark, BSc, MD, FRCP, Consultant Physician, Guy's and Brompton Hospitals; Professor of Thoracic Medicine, Guy's Hospital Medical School, London. Cassell Ltd, 35 Red Lion Square, London WCIR 4SG, 1980. 188 pages.

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(Continued from Page 23)

October 29-31—**Cardiology Update—1981.** American College of Cardiology and UCSF at Quail Lodge, Carmel Valley. Thursday-Saturday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

November 6-8—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 6-8—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 7—**Neurological Assessment.** PMC. Saturday. 6 hrs.

November 11—**Acid Base Disorders.** LLU. Wednesday.

November 14—**Clinics in Medicine—Nephrology/Hypertension.** PMC. Saturday. 3 hrs. $40.

November 14—**Modern Drug Management of Common Pulmonary Diseases.** UCSF at Fresno. Saturday. Contact: Kathleen Wolff, Area Health Education Ctr., 5110 E. Clinton Way, Suite 201, Fresno 93727. (209) 252-1948.

November 16-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** Am. College of Allergists, Sociedad Mexicana de Allergia E Immunologia, Autonoma Univ. of Baja and UCSD at San Diego (16-18) and Tijuana (19-20). Monday-Friday. 21 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

December 11-13—**Cardiology for the Primary Care Physician.** UCD. Friday-Sunday.

December 12—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

January-March—**Endocrinology for the Practicing Internist.** UCLA. Wednesday evenings.

January 9—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 16-23—**Nephrology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $425.

January 20-22—**Conference on Nephrology.** UCSD at Hilton, San Diego. Wednesday-Friday.

January 27-29—**Echocardiography: An Introductory Course for the Practicing Physician.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2-6—**What Is Ahead in Lung Diseases for the 80's.** USC at Death Valley. Tuesday-Saturday.

February 3-5—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 6—**Clinics in Medicine—Rheumatology.** PMC. Saturday. 3 hrs. $40.

February 15-17—**Recent Advances in Clinical Endocrinology.** UCSF. Monday-Wednesday.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 18-20—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

OBSTETRICS AND GYNECOLOGY

October 14-18—**Pacific Coast Fertility Society—29th Annual Scientific Meeting and Postgraduate Courses.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: Dir. of Med. Ed., PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

October 17—**Preventing Birth Defects.** UCD and March of Dimes at Sierra Inn, Sacramento. Contact: UCD.

October 26-30—**11th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 7-9—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 14-16—**Perinatology.** UCSD at Holiday Inn at Embarcadero, San Diego. Monday-Wednesday.

January 9-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $395.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

February 6-7—**Los Angeles OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 8-12—**37th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

PEDIATRICS

September 23-24—**38th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday-Thursday. Contact: LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 25-29—**Pediatric Urology.** UCD at Silverado Country Club, Napa. Friday-Tuesday.

October 2-3—**Pediatric Gastroenterology and Nutrition.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 10 hrs.

October 9-11—**Blood Diseases and Cancer in Children.** STAN at Children's Hospital at Stanford. Friday-Sunday.

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

October 23-24—**New Directions in Care for the Handicapped Child.** State Dept. of Special Education and Northern Calif. Chap., Am. Academy of Pediatrics, at Fresno Community Hospital, Fresno. Friday-Saturday. $75. Contact: Peter Miller, MD, Marin Civic Ctr., Rm. 280, San Rafael 94903. (415) 499-6877.

October 23-24—**The Pediatrician's Role in the Management of Neurological and Neurosurgical Problems.** Children's Hospital Medical Center of Northern Calif. at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

October 24—**Pediatric Seminar, Asthma: Principles and Management.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 453-8696 or (916) 486-2690.

December 4-6—**Kids Have Bones, Too.** UCD. Friday-Sunday.

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

PSYCHIATRY

September 29-30—**Review of Pathological States of Adolescence.** Center for Mental Health Training/North, Emeryville. Tuesday-Wednesday. 12 hrs. Contact: Ctr. for Mental Health Training, 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

September 29-October 1—**Sexual Abuse of Children Within the Family.** Center for Mental Health Training/North, Emeryville. Tuesday-Thursday. 18 hrs. $80. Contact: Ctr. for Mental Health Training, 5850 Shellmound St., Suite 390, Emeryville 94608. (415) 464-0685.

October 22-23—**Mental Health Issues of the Individual with a Developmental Disability—An Intensive Seminar on Treatment Techniques and Strategies.** Hope Rehabilitation Services and San Jose State Univ. at Rickey's Hyatt House, Palo Alto. Thursday-Friday. Contact: Bonnie Bernell or Fay Sells, HRS, 1539 Parkmoor Plaza, San Jose 95128. (408) 998-4673.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** UCD at Red Lion Inn, Sacramento. Saturday. 7¼ hrs. $75.

January 21-26—**Psychiatric Symposium.** Continuing Medical Education, Inc., and Western Medical Center at Maui Surf Resort, Maui. Thursday-Tuesday. 24 hrs. Contact: CME, Inc., 2030 E. 4th St., #113, Santa Ana 92705. (714) 547-5186.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

RADIOLOGY AND PATHOLOGY

September 19—**8th Annual Radiology Symposium.** So. Calif. Permanente Medical Group at Hilton Hotel, Los Angeles. Saturday. Contact: Felecia Madison, SCPMG, Education and Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

September 25-26—**The Dematiaceous Fungi: Clinical and Laboratory Identification.** UCSF. Friday-Saturday. 7½ hrs. $125.

October 2—**Uroradiology Seminar.** Orange Co. Urological Soc. and Western Section, American Urological Assn., at South Coast Plaza Hotel, Costa Mesa. Friday. $100. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

October 8-9—**Fine Needle Aspiration of Breast and Thyroid.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. 13 hrs.

October 8-10—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. $100, before Sept. 15; $125, thereafter. Contact: Dr. Luis M. de la Maza, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

October 9-10—**Mycology Review.** See Medicine, October 9-10.

October 10-18—**6th Annual International Body Imaging Conference.** West Park Hospital and American College of Radiology at Hyatt Regency, Maui. 9 days. 25 hrs. $365. Contact: West Park Hosp., Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 29-30—**Laboratory Diagnosis in Clinical Practice.** UCSF. Thursday-Friday.

October 31—**GYN Pathology.** USC. Saturday. 6 hrs. $60.

November 24—**Use of Antimicrobial Agents Old and New.** UCD at Red Lion Inn, Sacramento. Tuesday.

February 3-5—**New Directions in Clinical Laboratory Assays: 4th Immunology Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 18 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 10—**Pulmonary Function Tests and Blood Gas Interpretation.** LLU. Wednesday. 4 hrs. $30.

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SURGERY

September 18-19—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

September 19—**Oxygen Transmission and Extended Wear Contact Lenses.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

September 25-29—**Pediatric Urology.** See Pediatrics, September 25-29.

September 26—**Early Care of the Critically Injured Patient.** Southern Calif. Division of U.S. Section of International College of Surgeons at Los Angeles Co. Med. Assn., Los Angeles. Saturday. Contact: George Evashwick, MD, 204 Roswell Ave., Long Beach 90803.

October 2—**Medical Malpractice in Ophthalmology—A Review of Common Diagnostic and Therapeutic Errors.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. 8 hrs. $50. Contact: Margaret Frederick, Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 2—**Uroradiology Seminar.** See Radiology and Pathology, October 2.

October 2-3—**Cataract Surgery and Intraocular Lenses Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

October 3-10—**3rd International Seminar on Operative Arthoscopy.** UCLA at Maui. One week.

October 9-10—**Annual Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $225.

October 11-16—**American College of Surgeons—67th Annual Clinical Congress.** Fairmont and Hilton Hotels, San Francisco. Sunday-Friday. Contact: Fred C. Spillman, Convention Mgr., ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

October 15-17—**New Horizons in Knee and Hip Surgery.** UCLA. Thursday-Saturday.

October 16-17—**Fracture Bracing Workshops.** USC at University Hilton, Los Angeles. Friday-Saturday. 17 hrs. $375.

November 7-8—**Clinical Application of Evoked Potentials.** UCSF. Saturday-Sunday.

November 11-15—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** Institute for Medical Education and Research at Silverado County Club, Napa. Wednesday-Sunday. 20 hrs. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

November 11-15—**The Spine.** USC at Canyon Hotel, Palm Springs. Wednesday-Sunday. $400.

November 12-14—**Techniques in Urinary Tract Surgery.** American Urological Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611.

November 17-20—**U.S. Section of International College of Surgeons.** Hotel del Coronado, Coronado. Tuesday-Friday. Contact: George Evashwick, MD, 204 Roswell Ave, Long Beach 90803.

December 2-4—**Invasion of the Cornea and Lens.** UCSF. Wednesday-Friday.

December 3-6—**Bone Grafting: Biology and Application.** Plastic Surgery Research Foundation at Hyatt Islandia, San Diego. Thursday-Sunday. 17 hrs. $275. Contact: Jack C. Fisher, MD, P.O. Box 33387, San Diego 92103.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

January 15-16—**Vitrectomy Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Stereotactic Vitreous Microsurgery.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

February 10-12—**Traumatic and Congenital Hand Surgery.** UCLA. Wednesday-Friday.

February 28-March 3—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Wednesday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

OF INTEREST TO ALL PHYSICIANS

September 19-20—**Eating Disorders.** UCLA. Saturday-Sunday.

September 21-23—**Spectrum of Recovery: From Conception Through the Golden Years.** Scripps Memorial Hospital, Alcoholism Treatment Center, at Islandia Hyatt, San Diego. Monday-Wednesday. 15 hrs. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 21-24—**American Academy of Family Physicians.** Convention Center, Las Vegas. Monday-Thursday. 30+ hrs. Contact: Edward E. Daleske, Sec., Committee on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

September 27-30—**Sports Medicine Now.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Wednesday. 22½ hrs. $200.

October 3—**2nd Annual Hyperbaric Symposium.** Sutter Community Hospitals at Holidome, Sacramento. Saturday. 7 hrs. Contact: Kristie Grieves, (916) 454-2222, ext. 1673.

October 7-10—**1981 Western Occupational Health Conference.** Western Occupational Medical Assn. at Doubletree Inn, Monterey. Wednesday-Saturday. Contact: Joseph Donovan, Exec. Dir., WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 12-13—**Alcoholism and the Family.** PMC at Sheraton at Fisherman's Wharf, San Francisco. Monday-Tuesday. 12 hrs. $85.

October 12-16—**Clinical Update.** American Medical Assn. at Ilikai Hotel, Honolulu. Monday-Friday. Contact: Dept. of Meeting Services, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

October 12-16—**Hawaii Medical Association—Annual Meeting.** Ilikai Hotel, Honolulu. Monday-Friday. Contact: HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 16—**2nd Annual Neurosciences Symposium: Current Concepts for Non-Neurologists.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

October 17-18—**The Healing Brain: Who Stays Healthy.** UCSF Cont. Ed. in Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 19-22—**British Medical Association Congress.** Town and Country Hotel, San Diego. Monday-Thursday. 10 hrs. through UCSD. Contact: Mr. G. Denney, Assoc. Exec. Dir., San Diego Co. Med. Soc., 3702 Ruffin Rd., San Diego 92123. (714) 565-8888.

October 22-24—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** See Psychiatry, October 24.

October 24-25—**5th Annual Symposium on Aging.** UCSF Cont. Ed. in Health Sciences at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 25-28—**California Academy of Family Physicians—Annual Meeting.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: William Rogers, CAFP, 9 First St., Rm. 900, San Francisco 94105. (415) 982-6091.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

October 31—**Introduction to Traditional Chinese Medicine.** PMC. Saturday. 7 hrs. $125.

November 1-5—**American Public Health Association—109th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Thursday. Contact: APHA, 1015 15th St., NW, Washington DC 20005.

November 1-6—**American Congress of Rehabilitation Medicine and American Academy of Physical Medicine and Rehabilitation.** Town and Country, San Diego. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., 30 N. Michigan Ave., Suite 922, Chicago 60602. (312) 236-9512.

November 2-6—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $325.

November 10-February 9—**Foundations of Traditional Chinese Medicine.** PMC. Tuesday evenings.

November 14-15—**In Pursuit of Wellness.** UCSF Cont. Ed. in Health Sciences at UCLA. Saturday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

November 15—**Dilemmas With Drugs in Clinical Practice.** Granada Hills Community Hospital and UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 16-20—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

December 4—**Nutritional Support: The Challenge for the Seriously Ill Patient.** Daniel Freeman Memorial Hospital and Marina Mercy Hospital at Daniel Freeman Mem. Hosp., Inglewood. Friday. 7 hrs. $60. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Mem. Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 3427.

December 4-11—**Behavioral Medicine and Primary Care in the 80's.** Professional Institutes and Univ. of So. Carolina School of Medicine at Ilikai Hotel, Honolulu. One week. 16 hrs. $300. Contact: Jeri McClain, USC School of Medicine, Office for Academic Affairs, Columbia, SC 29208. (803) 777-7470.

January 16—**Herpes Simplex: Clinical Practice and Research.** UCSF Cont. Ed. in Health Sciences at Fort Mason Conference Center, San Francisco. Saturday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 3-5—**Neurology for Non-Neurologists.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 6-7—**Immunology for the Family Physician.** UCLA. Saturday-Sunday.

February 7-12—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Friday.

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

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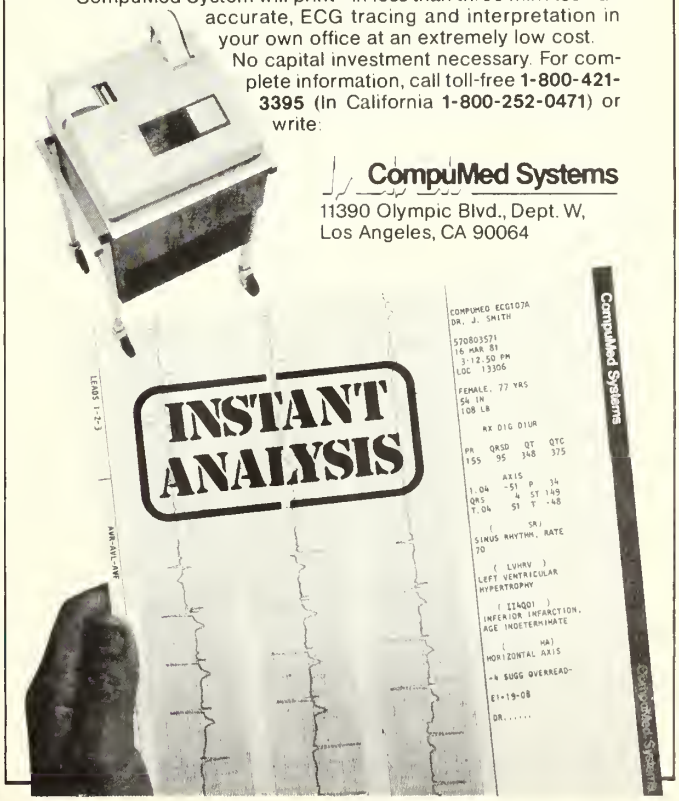

maries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category 1 hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

MONTANA

October 1-3—**Annual Meeting of the Montana Medical Association.** Butte. Thursday-Saturday. Copper King Inn. Contact: Montana Medical Association, 2020 11th Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 26—**Stroke and Spinal Cord Injuries.** Roswell. Saturday. Roswell Inn. 7 credit hours. Contact: W. J. Dean, MD, 813 North Washington, Roswell, NM 88201. (505) 622-2606.

September 27-October 1—**Southwest Obstetrical & Gynecological Society 1981 Annual Meeting.** Santa Fe. Sunday-Thursday. Inn at Loretto. 30 credit hours, also AAFP Prescribed. Contact: W. Duane McCarty, MD, 5400 Gibson SE, Albuquerque, NM 87108. (505) 842-7291.

October 3—**Primary Care and Mental Health.** Albuquerque. Saturday. Sheraton Old Town Inn. 6 credit hours, also AAFP Prescribed. Contact: John C. McCormack, MD, Vista Sandia Hospital, 501 Richfield NE, Albuquerque, NM 87113. (505) 898-1661.

October 9-10—**Southwest Regional Diabetes Symposium.** Albuquerque. Friday-Saturday. Albuquerque Hilton Inn. 8 credit hours. Contact: David Feirer, New Mexico Affiliate Inc., American Diabetes Association, 525 San Pedro Drive, NE, Suite 100, Albuquerque, NM 87108. (505) 266-5716.

October 22-24—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: Barry W. Ramo, MD, 201 Cedar SE, Albuquerque, NM 87106. (505) 242-2796.

October 30—**Infectious Disease Update 1981.** Albuquerque. Wednesday. 4 credit hours, also AAFP Prescribed. Contact: Martha McPherson, Pfizer Laboratories Division, Pfizer Inc., 235 East 32nd Street, New York, NY 10017, (212) 573-7285; Or New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 6—**Los Alamos Council for Cancer Annual Symposium for Colon Cancer.** Los Alamos. Friday. 16 credit hours. Contact: Philip H. Newman, MD, FACS, Los Alamos Surgical Associates Ltd., Los Alamos, NM 87544. (505) 662-3383.

November 13-14—**Interium Meeting, New Mexico Medical Society.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Scientific Program to be announced. Contact: New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 17-21—**The Grand Canyon Conference on the Treatment of Addictive Behaviors.** South Rim of Grand Canyon. Tuesday-Saturday. Grand Canyon National Park Lodges. Hour-for-hour credit. Contact: T. P. Bouble, Conference Coordinator, Division of Continuing Education & Commity Services, University of New Mexico, Albuquerque, NM 87131. (505) 277-2931.

OREGON

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health

Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 1-3—**Fifth Annual Pacific NW Review of Obstetrics & Gynecology.** Thursday-Saturday. Thunderbird-Jantzen Beach, Portland, Oregon. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

OPHTHALMOLOGY

October 1-2—**Vitrectomy.** Thursday-Saturday. Oregon Health Sciences University, Portland. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

SURGERY

November 20—**Soft Tissue Surgery Techniques.** Friday. Oregon Health Sciences University, Portland. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

September 11-12—**Gastroenterology: Current Concepts in Colon Disorders, Hepatitis and Obstructive Jaundice.** Friday-Saturday. Ashland Hills Inn, Ashland, Oregon. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

September 25—**Second Annual Poisoning & Toxicological Emergencies Conference.** Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

November 12-13—**Symposium on Critical Care Medicine.** Thursday-Friday. Red Lion at Jantzen Beach, Portland. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

December 4-5—**Urology for the Non-Urologist.** Friday-Saturday. Red Lion-Downtown, Portland. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

September 9-11—**Utah State Medical Association 86th Annual Scientific Session** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. 12 hrs. Fee: $50. Contact: Maxcine Fry (801) 355-7477.

September 12—**Exercise and Health** (Sponsors: 328th General Hospital, USAR at Ft. Douglas/Surgeon General's Office, US Army). Salt Lake City. Saturday. Hotel Utah. 6 hrs. Fee: $25. Contact: Kent Porter, Major, MCS (801) 582-4181.

September 25-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Sunday. Tri-Arc Travelodge. 17 hrs. Fee: $300. Contact: Tricia Neilson, RN (801) 533-6435.

October/November—**Medical Effects of a Nuclear War** (Sponsor: University of Utah). Salt Lake City. Date: To be announced. University of Utah campus. Credit, Fee: To be announced. Contact: Chase N. Peterson, MD (801) 581-5619.

October 9—**Topics in Pharmacology—Regional Joint ACP-ASIM Meeting** (Sponsors: University of Utah/American College of Physicians). Salt Lake City. Friday. Hilton Hotel. Hrs. to be announced. Fee: $20. Contact: Gregory A. Schwitzer, MD (801) 581-7818.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

October 16-27—**Western Mediterranean Air/Sea Cruise and Medical Seminar** (Sponsors: Washington University School of Medicine (St. Louis)/Utah State Medical Association). Portugal, Morocco, Gibraltar, Spain, Italy, France. Friday-Tuesday. 27 hrs. Fee: $250 (Medical Seminar Registration Only). Contact: Maxcine Frey (801) 355-7477.

November 2-7—**Training and Certification of Pulmonary Function Testing** (Sponsor: University of Utah). Location to be announced. Monday-Saturday. 17.5 hrs. Fee: To be announced. Contact: P. Lockey, MD (801) 581-3455.

November 6—**Renal/Pulmonary Syndrome — Postgraduate Course** (Sponsor: LDS Hospital). Salt Lake City. Friday. Hotel Utah. Hrs. and Fee to be announced. Contact: C. DuWayne Schmidt, MD (801) 350-1813.

November 13-14—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Tri-Arc Travelodge. 17 hrs. Fee: $300. Contact: Tricia Neilson, RN (801) 581-7617.

December 4-5—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 17 hours. Fee: $300. Contact: Tricia Neilson, RN (801) 533-6435.

December 10-12—**Informed Consent Conference** (Sponsor: University of Utah). Thursday-Saturday. Location, Credit, Fee: To be announced. Contact: Albertha Western (801) 581-6233.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 19 hrs. Fee: $200-$225. Contact: John L. Ninnemann, PhD (801) 581-7617.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Friday-Tuesday. Location, Credit: To be announced. 16 hours. Contact: T. Stanley, MD (801) 581-6393.

February 21-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Sunday-Tuesday. The Yarrow. 15 hours. Fee: To be announced. Contact: David Engleberg (801) 581-3087.

February 24-27—**Endocrinology Update OB/GYN** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 15 hours. Fee To be announced. Contact: David Engleberg (801) 581-3087.

March 14-21—**8th Annual Park City Lacrimal Course** (Sponsor: University of Utah). Park City. Sunday-Sunday. 20 hours. Fee: To be announced. Contact: Darrel Wolfley, MD (801) 363-3355.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

September 10-12—**Plastic Surgery for Primary Physicians.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: U/W School of Medicine.

September 15—**Gram Negative Infections and Antibiotics.** Seattle. Tuesday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext 1737.

September 16—**Spokane Internal Medicine Review.** Spokane. Wednesday evening. Sacred Heart Medical Center. Contact: U/W School of Medicine.

September 17-18—**Immediate Care of the Sick and Injured.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: U/W School of Medicine.

September 18—**Progress in Breast Cancer.** Seattle. Friday. Providence Medical Center. Contact: Evelyn Foote, Physician Education, Providence Medical Center, 500 17th Avenue C-34008, Seattle, WA 98124. (206) 326-5555.

September 21-22—**Critically Ill Surgical Patient.** Seattle. Thursday-Friday. UW Health Sciences Building. Contact: UW School of Medicine.

September 21-25—**Advances in Family Practice.** Seattle. Monday-Friday. UW Kane Hall. Contact: U/W School of Medicine.

September 24—**The Learning Disabled Child: The Educator-Physician Team and Its Approach.** Lynnwood. Thursday. Landmark Inn. Contact: Sheri Lindquist, Medical Education Coordinator, Snohomish County Medical Education Board, PO Box 1147, Everett, WA 98206. (206) 258-6322.

September 25-26—**Annual Scientific Program: Washington State Medical Association Annual Meeting.** Spokane. Friday-Saturday. Davenport Hotel. Contact: Marcia Wahlman, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801, or in-state toll-free at 1-800-552-0612.

September 26—**Orthopedics/Rheumatology.** Tacoma. Saturday. Contact: CME Pierce County.

October 1-3—**Advanced Cardiac Life Support.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

October 3—**Fifth Annual Cancer Symposium.** Tacoma. Saturday. Jackson Hall Medical Center Auditorium. Contact: Karen Tilley, Department of Oncology, Tacoma General Hospital, 315 South K Street, Tacoma, WA 98405. (206) 597-6965.

October 7-11—**Cytology Continuing Education Workshop.** Honolulu. Wednesday-Sunday. Contact: CME Harborview.

October 15—**Enhancing Clinical Skills in Counseling Lesbian and Gay Clients and Their Families.** Seattle. Thursday. University of Washington—HUB. Contact: Seattle Counseling Service, 1505 Broadway, Seattle, WA 98122. (206) 329-8737.

October 15-16—**Obstetrics for the 80's.** Everett. Thursday-Friday. Everett Community College. Contact: Sheri Lindquist, Medical Education Coordinator, Snohomish County Medical Education Board, PO Box 1147, Everett, WA 98206. (206) 258-6322.

October 16-18—**Cytology Continuing Education Workshop.** Anchorage, Alaska. Friday-Sunday. Contact: CME Harborview.

October 29-30—**Degenerative Joint Disease.** Seattle. Thursday-Friday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

November 7—**The Care of Aging Patients.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed

(Continued on Page 46)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

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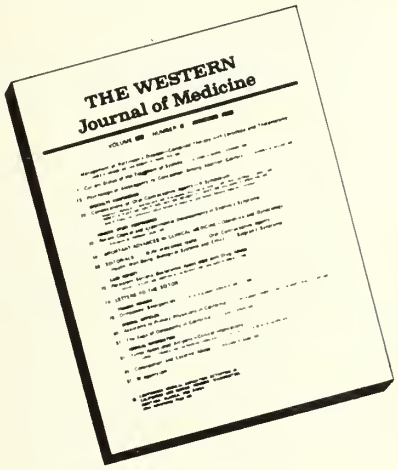

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Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: May 26-30, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 9-12, 1981, Keystone.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1982—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 8-11, 1981, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: September 24-27, 1981, Davenport Hotel, Spokane.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Midwinter Seminar January 7-9, 1982, Teton Village, Jackson. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

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Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

November 7—**Medical Ethics.** Tacoma. Saturday. Contact: CME Pierce County.

December 10-12—**Cytology Continuing Education Workshop.** Spokane. Thursday-Saturday. Contact: CME Harborview.

January 21-23—**Cytology Continuing Education Workshop.** Portland, OR. Thursday-Saturday. Contact: CME Harborview.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 15-17—**Cytology Continuing Education Workshop.** Billings, MT. Thursday-Saturday. Contact: CME Harborview.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

August 19-21—**Cytology Continuing Education Workshop.** Eugene, OR. Thursday-Saturday. Contact: CME Harborview.

September 16-18—**Cytology Continuing Education Workshop.** Jackson, WY. Thursday-Saturday. Contact: CME Harborview.

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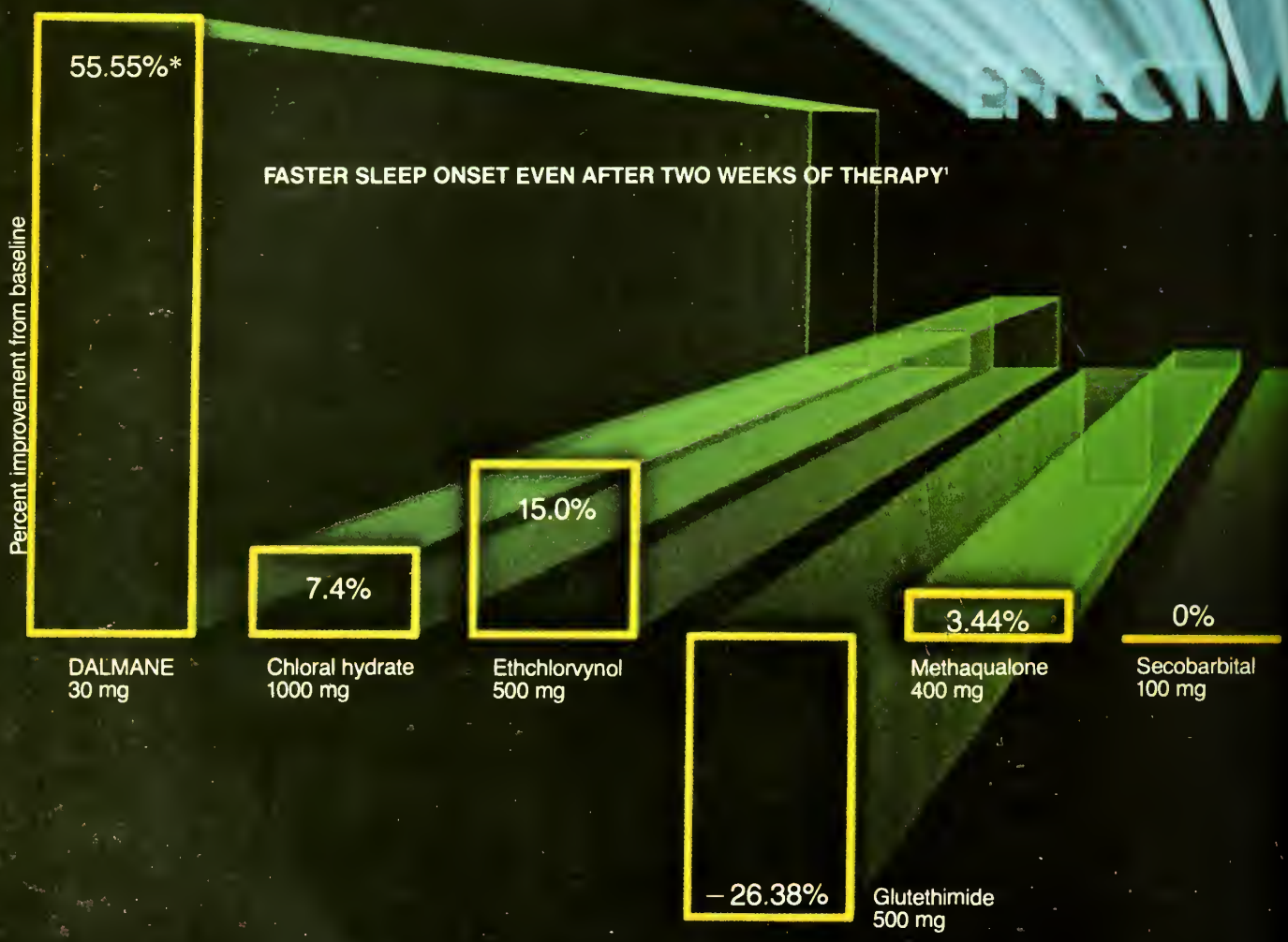

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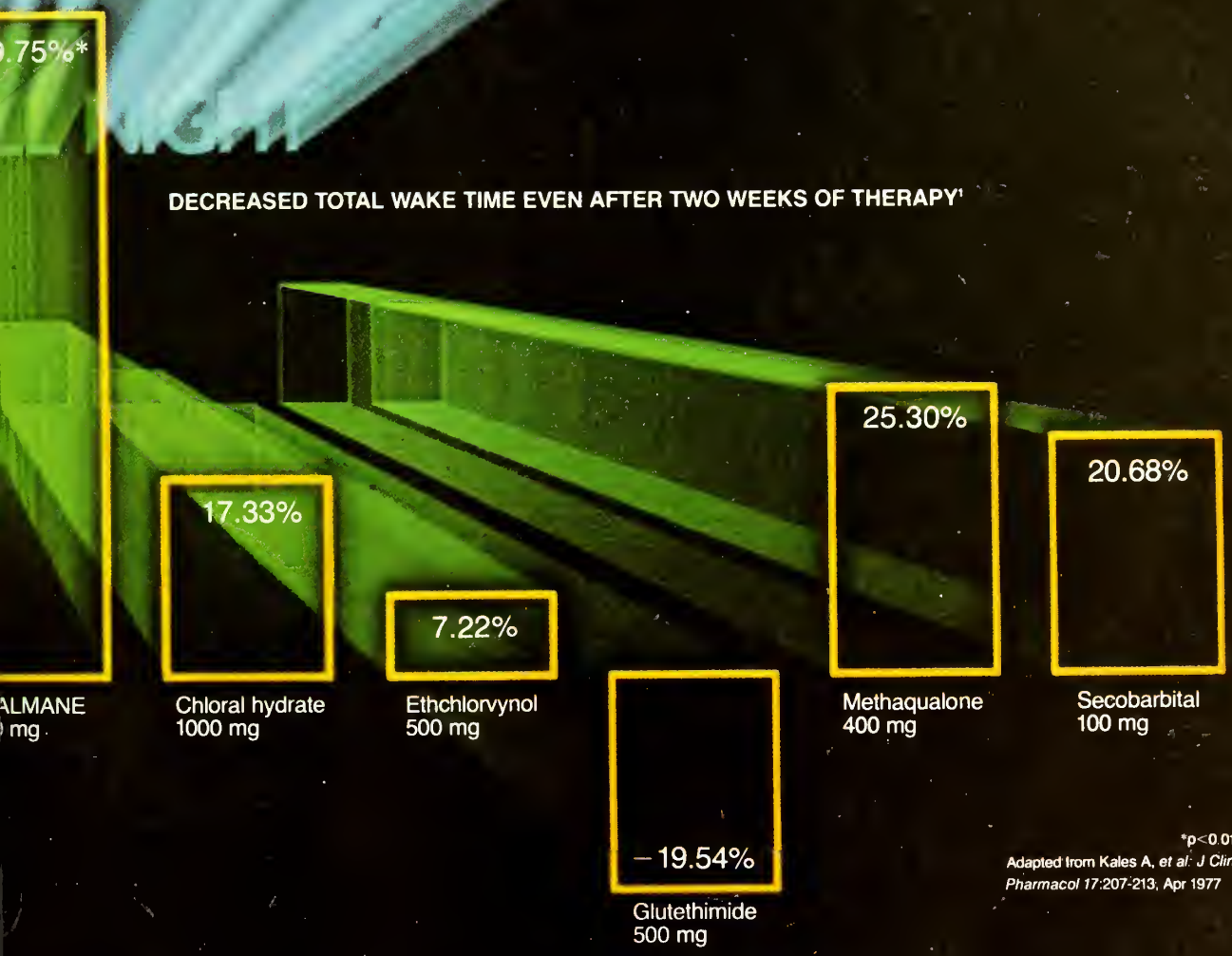

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–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

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–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

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–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane does not cause significant worsening of sleep beyond baseline levels upon discontinuation.[8]

References. **1.** Kales A, *et al J Clin Pharmacol 17* 207-213, Apr 1977 **2.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **3.** Greenblatt DJ, Allen MD, Shader RI. *Clin Pharmacol Ther 21*:355-361, Mar 1977 **4.** Moore JD, Weissman L: *J Clin Pharmacol 16*:241-244, May-Jun 1976 **5.** Spiegel HE: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **6.** Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, pp 641-646 **7.** Warfarin Study: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **8.** Kales A, *et al Clin Pharmacol Ther 18*:356-363, Sep 1975 **9.** Baldessarini RJ: Drugs and the treatment of psychiatric disorders, chap. 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp 391-447 **10.** Cole JO, Davis JM: Antidepressant drugs, chap. 31.2, in *Comprehensive Textbook of Psychiatry II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp 1941-1956 **11.** Douglas WW: Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6. New York, Macmillan Publishing Co. Inc., 1980, pp 609-646 **12.** Davis JM, Cole JO: Antipsychotic drugs, chap. 31.1, in *Comprehensive Textbook of Psychiatry/II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2. Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp. 1921-1940

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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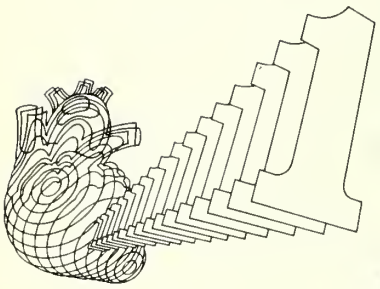

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

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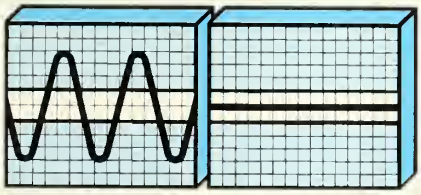

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Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk Incidence of toxicity increases at serum levels greater than 20 mcg/ml High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions Ventricular arrhythmias or seizures may be the first signs of toxicity Many patients who have higher theophylline serum levels exhibit a tachycardia Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established This is, unfortunately, true for most anti-asthmatic medications Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves Use theophylline cautiously in patients with history of peptic ulcer Theophylline may occasionally act as a local irritant to G I tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are

Gastrointestinal Nausea, vomiting, epigastric pain, hematemesis, diarrhea

Central Nervous System Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions

Cardiovascular Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.

Respiratory Tachypnea

Renal Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis

Others Hyperglycemia and inappropriate ADH syndrome.

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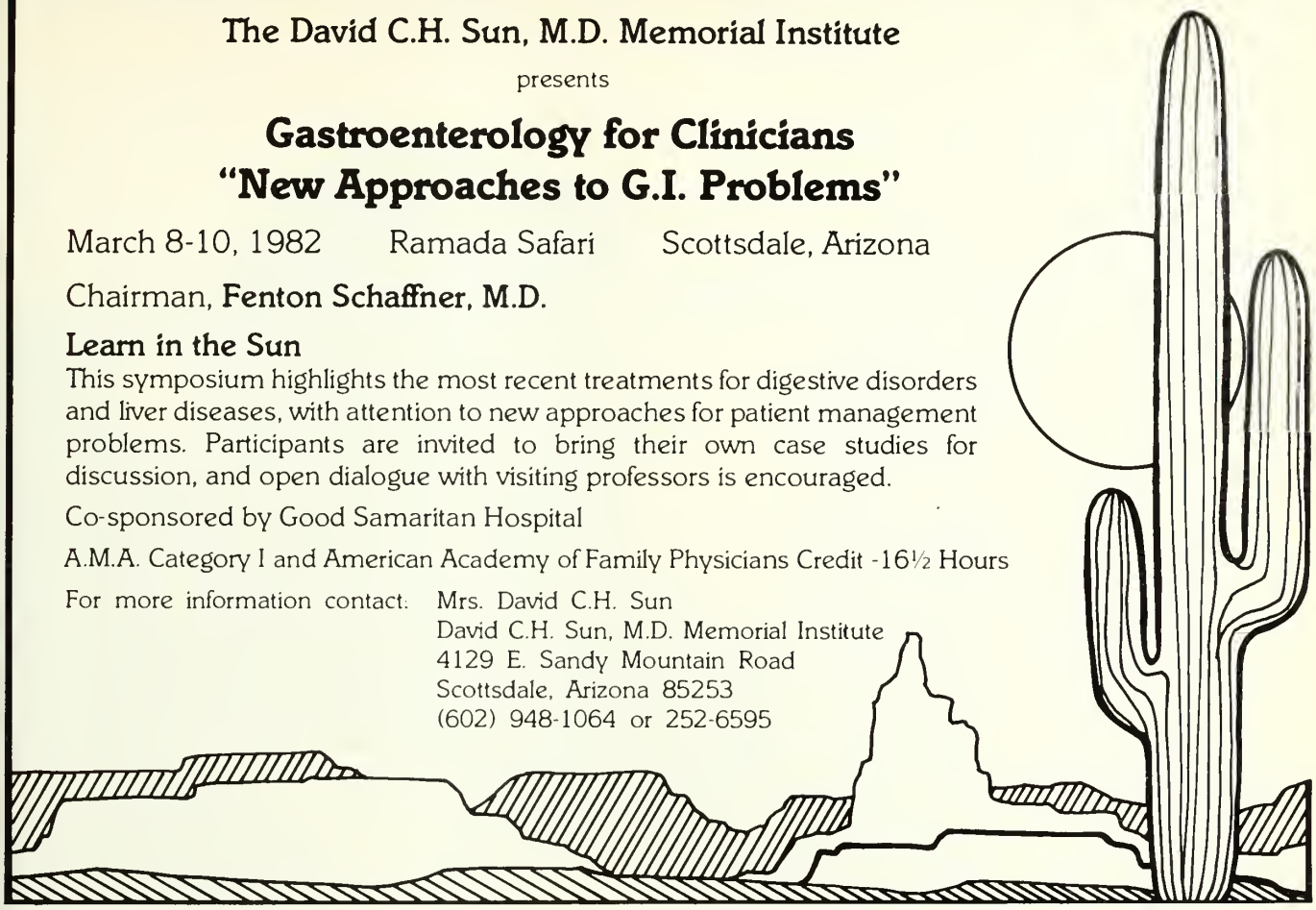

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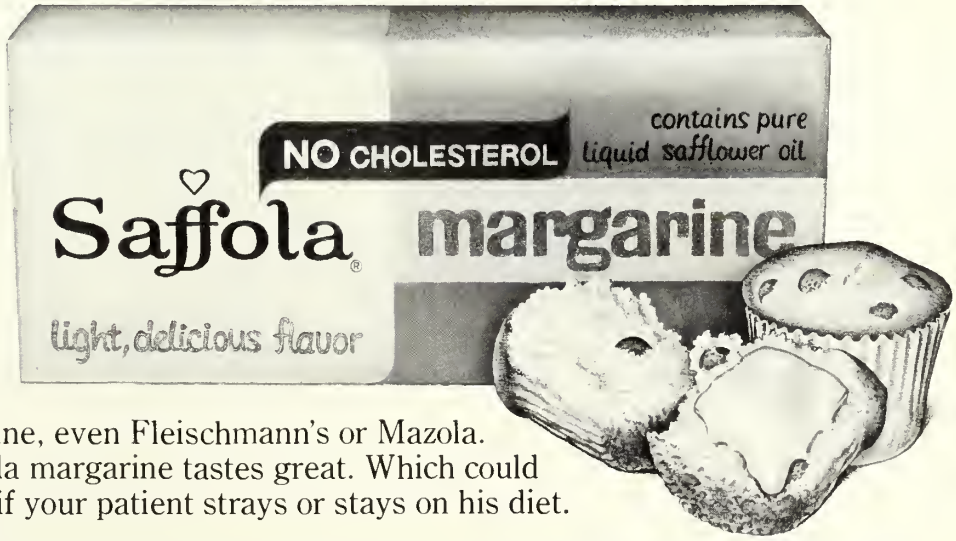

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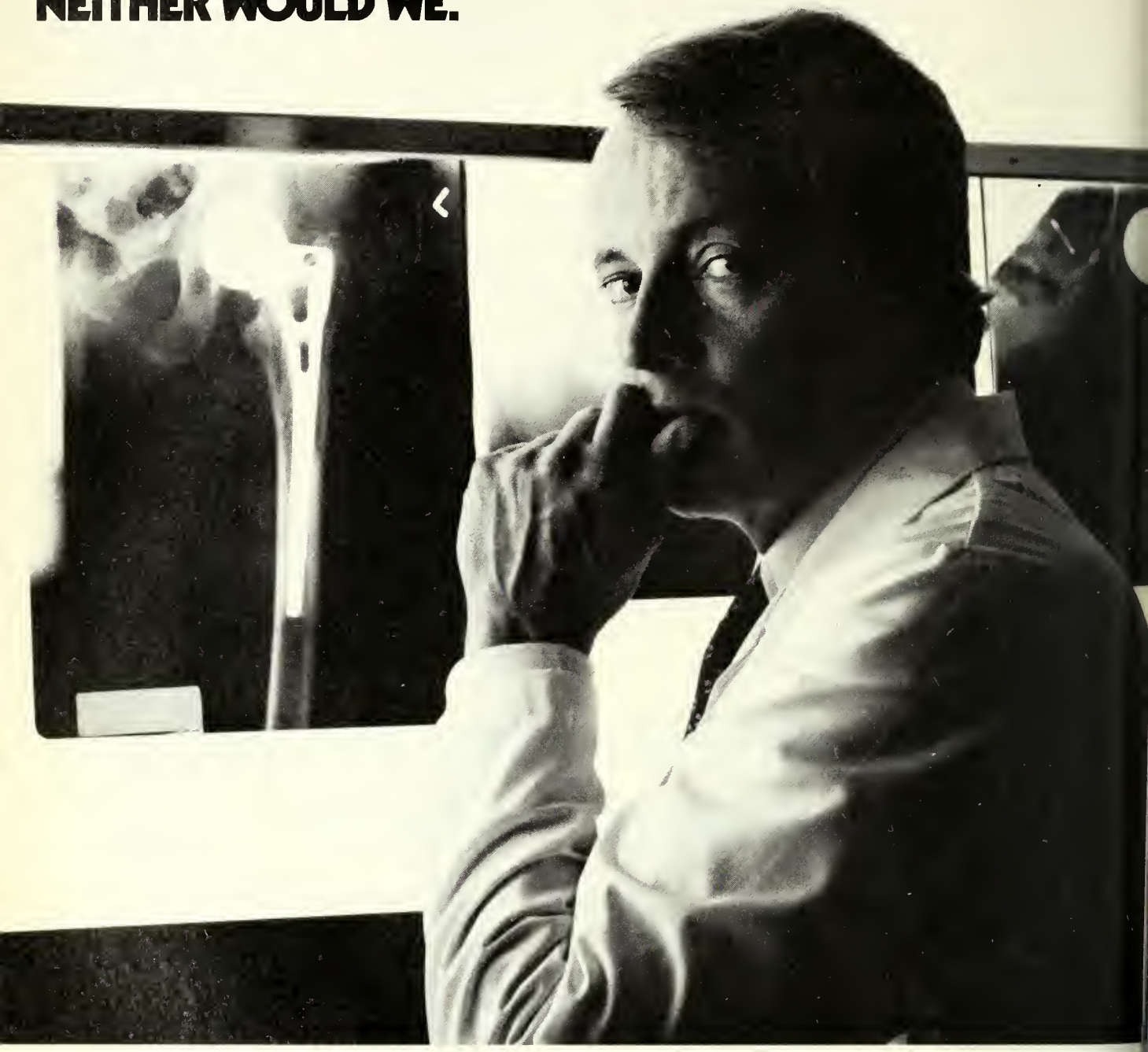

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So patients take only three tablets a day instead of four, which may enhance patient compliance.

In fasting subjects, the new *E-Mycin* 333 mg q8h regimen has been shown to be bioequivalent to 250 mg of erythromycin base administered q6h.

While the most frequent side effects of erythromycin are gastrointestinal, the new *E-Mycin* 333 mg tablets caused no more gastrointestinal side effects than *E-Mycin* 250 mg tablets in a controlled study involving healthy adults.

See following page for brief summary of prescribing information.

Upjohn

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Indications: *Streptococcus pyogenes (group A beta-hemolytic streptococci):* Upper and lower respiratory tract, skin, and soft-tissue infections of mild to moderate severity. Therapy should be continued for ten days. Parenteral benzathine penicillin G is the drug of choice.
Alpha-hemolytic streptococci (viridans group): Short-term prophylaxis against bacterial endocarditis prior to dental procedures or surgery of the upper respiratory tract in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin. Erythromycin is not suitable prior to genitourinary surgery.
Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistance may develop during treatment.
Streptococcus pneumoniae: Upper respiratory tract infections (eg, otitis media, pharyngitis) and lower respiratory tract infections (eg, pneumonia) of mild to moderate degree.
Mycoplasma pneumoniae (Eaton agent, PPLO): For respiratory infections due to this organism.
Treponema pallidum: An alternative treatment for penicillin-allergic patients.
Corynebacterium diphtheriae and *Corynebacterium minutissimum:* An adjunct to antitoxin, to prevent or treat carriers. In the treatment of erythrasma.
Entamoeba histolytica: Intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.
Listeria monocytogenes: Infections due to this organism.
Neisseria gonorrhoeae: In conjunction with erythromycin lactobionate injection in patients allergic to the penicillins. Patients should have a microscopic examination for *T. pallidum* (by immunofluorescence or darkfield).
Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity, in combination with sulfonamides. Not all strains are susceptible.
Bordetella pertussis: Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.
Legionnaires' disease: In vitro and limited clinical data suggest efficacy. Establish susceptibility of organisms to erythromycin.
Contraindication: Known hypersensitivity to erythromycin.
Warning: Safety for use in pregnancy has not been established.
Precautions: Erythromycin is principally excreted by the liver. Exercise caution in patients with impaired hepatic function. Hepatic dysfunction, with or without jaundice, has occurred with oral erythromycin products. Surgical procedures should be performed when indicated. Concurrent use with theophylline may potentiate theophylline toxicity. Theophylline dosage should therefore be reduced.
Adverse Reactions: The most frequent side effects are gastrointestinal, eg, abdominal cramping and discomfort, and are dose related. Nausea, vomiting, and diarrhea occur infrequently. During prolonged or repeated therapy, nonsusceptible bacteria or fungi may overgrow. The drug should then be discontinued and appropriate therapy instituted. Urticaria and other skin rashes have occurred. Serious allergic reactions, including anaphylaxis, have been reported.
How Supplied: E-MYCIN Tablets 333 mg—in bottles of 100. E-MYCIN Tablets 250 mg—in bottles of 100, 500, and unit-dose packages (100).
Caution: Federal law prohibits dispensing without prescription.
For additional product information, consult the package insert or see your Upjohn Representative. B-12-S

The Upjohn Company, Kalamazoo, Michigan 49001

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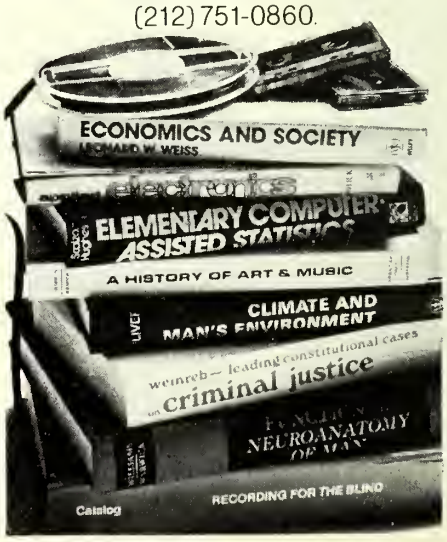

CONTINUING MEDICAL EDUCATION

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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 139. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

January 10-15—**Anesthesiology Update.** UCSD. Sunday-Friday.

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-18—**International Anesthesia Research Society—56th Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: International Anesthesia Research Soc., 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

CANCER

October 23—**DES Update 1981.** Adult Health Section of Calif. Dept. of Health Services and Calif. Div., American Cancer Soc. at Hyatt, Burlingame. Friday. 6 hrs. $60. Contact: Cancer Control Unit, Adult Health Section, Dept. of Health Services, 714 P St., Rm. 499, Sacramento 95914. (916) 322-4787.

October 26-28—**Fifth Annual Cancer Symposium.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. 22 hrs. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 30—**DES Update 1981.** Adult Health Section of Calif. Dept. of Health Services and Calif. Div., American Cancer Soc., at Hacienda Hotel, El Segundo. Friday. 6 hrs. $60. Contact: Cancer Control Unit, Adult Health Section, Dept. of Health Services, 714 P St., Rm. 499, Sacramento 95914. (916) 322-4787.

October 31—**4th Annual Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joann Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

October 31-November 1—**3rd Annual Symposium on Preventive Oncology: Cancer Prevention and Clinical Practice.** UCSF Continuing Education in Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

November 6—**Causes of Cancer.** Calif. Hospital Medical Center, Am. Cancer Soc., USC Cancer Management Network, at Biltmore Hotel, Los Angeles. Friday. $85. Contact: Kenneth Senter, MD, USC Comprehensive Cancer Ctr., 1721 Griffin Ave., Phinney Hall 105, Los Angeles 90031. (213) 742-5750.

November 13-14—**Current Concepts on Cancer Management: Successful Treatment and Its Consequences.** Mt. Zion Hospital and Medical Center at Fairmont Hotel, San Francisco. Friday-Saturday. 11 hrs. $150, before Sept. 15; $200, thereafter. Contact: Office of Cont. Med. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

February 27-28—**Breast Cancer: Conservation Surgery and Radiation Therapy Now—17th Annual San Francisco Cancer Symposium.** West Coast Cancer Fndn.; Am. Cancer Soc., Calif. Div.; St. Mary's Hosp. and Med. Ctr. at Sheraton Fisherman's Wharf, San Francisco. Saturday-Sunday. 12 hrs. $115 before Jan. 1; $140, thereafter. Contact: West Coast Cancer Fndn., 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

EMERGENCY MEDICINE

October 18-23—**Recognition and Management of Diving Casualties.** See Of Interest to All, October 18-23.

October 19-23—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

October 19-23—**Postgraduate Institute for Emergency Room Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $425.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling can't stop moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard bone loss*.. the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. That it's not intended to treat nervous symptoms or depression associated with the menopause. That it can be very helpful in treating symptoms related to estrogen deficiency. You know how to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she really needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for Brief Summary of Prescribing Information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)
2 Atrophic vaginitis
3 Kraurosis vulvae
4 Female hypogonadism
5 Female castration
6 Primary ovarian failure
7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8 Prostatic carcinoma—palliative therapy of advanced disease
9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression.[23,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention
b Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3 increased norepinephrine-induced platelet aggregability
c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered
d Impaired glucose tolerance
e Decreased pregnanediol excretion
f Reduced response to metyrapone test
g Reduced serum folate concentration
h Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e g three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K., *et al* N Engl J Med *293* 1167-1170, 1975 2 Smith, D C, *et al* N Engl J Med *293* 1164-1167, 1975 3 Mack, TM, *et al* N Engl J Med *294* 1262-1267, 1976 4 Weiss, N S, *et al*: N. Engl J. Med *294* 1259-1262, 1976 5 Herbst, A L, *et al* N Engl J. Med *284* 878-881, 1971 6 Greenwald, P, *et al* N Engl. J Med *285* 390-392, 1971 7 Lanier, A, *et al*. Mayo Clin Proc *48*:793-799, 1973 8 Herbst, A, *et al*: Obstet Gynecol *40*:287-298, 1972 9 Herbst, A, *et al* Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A, *et al* N Engl J Med *292*:334-339, 1975 11 Statl, A, *et al* Obstet Gynecol *43*:118-128, 1974 12 Sherman, A I., *et al* Obstet Gynecol *44* 531-545, 1974 13 Gal, I, *et al* Nature *216* 83, 1967 14 Levy, E P., *et al*: Lancet *1* 611, 1973 15 Nora, J., *et al* Lancet *1* 941-942, 1973 16 Janerich, D T., *et al* N Engl J Med *291* 697-700, 1974 17 Boston Collaborative Drug Surveillance Program: N Engl J Med *290* 15-19 1974 18 Hoover, R, *et al* N Engl J Med *295* 401-405, 1976 19 Daniel, D G., *et al* Lancet *2*:287-289, 1967 20 The Veterans Administration Cooperative Urological Research Group J Urol *98* 516-522, 1967 21 Ballar, J C Lancet *2*:560, 1967 22 Blackard, C., *et al*. Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J R Coll. Gen Pract *13* 267-279, 1967 23a Royal College of General Practitioners, Oral Contraceptives and Health, New York, Pitman Corp, 1974 24 Inman, W H W, *et al* Br Med J *2* 193-199, 1968 25 Vessey, M P., *et al* Br Med J *2* 651-657, 1969 26 Sartwell, P E., *et al* Am. J Epidemiol *90*:365-380, 1969 27 Collaborative Group for the Study of Stroke in Young Women N Engl J Med *288* 871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women J A M A *231* 718-722, 1975 29 Mann, J I., *et al*: Br Med J *2*:245-248, 1975 30 Mann, J.I., *et al* Br Med J *2* 241-245, 1975 31 Inman, W H W., *et al* Br Med. J *2*:203-209, 1970 32 Stolley, P D., *et al*: Am. J Epidemiol *102*:197-208, 1975 33 Vessey, M P, *et al*. Br Med J *3*:123-126, 1970 34 Greene, G R, *et al*: Am J Public Health *62* 680-685, 1972 35 Coronary Drug Project Research Group J A M A *214* 1303-1313, 1970 36 Mays, E T, *et al* J A M A *235*:730-732, 1976 37 Pfeffer, R I., *et al* Am J Epidemiol *103*:445-456, 1976

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(Continued from Page 19)

November 13—**Base Station Physician Symposium.** Calif. Chapter, Am. College of Emergency Physicians, at Valley Presbyterian Hospital, Van Nuys. Friday. 9 hrs. $125, ACEP members; $150, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., #240, Los Angeles 90045. (213) 776-1820.

November 23-24—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 12—**Managing Pediatric Emergencies.** See Pediatrics, December 12.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 5-6—**Base Station Physician Symposium.** Calif. Chapter, Am. College of Emergency Physicians, at Ahwahnee Hotel, Yosemite. Friday-Saturday. 9 hrs. $125, ACEP members; $150, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., #240, Los Angeles 90045. (213) 776-1820.

February 7-12—**Winter Sports Injuries.** See Of Interest to All, February 7-12.

February 12-13—**Toxicologic and Infectious Disease Emergencies.** UCLA. Friday-Saturday.

February 28-March 5—**Emergency Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 7-10—**Sports Injuries Update.** UCD at Hyatt, Lake Tahoe. Sunday-Wednesday.

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

MEDICINE

October 15-17—**Allergy/Immunology for the Practicing Physician.** UCSF. Thursday-Saturday.

October 16—**2nd Annual Neurosciences Symposium: Current Concepts for Non-Neurologists.** See Of Interest to All, October 16.

October 16-17—**Advances in Internal Medicine.** So. Calif. Permanente Medical Group at Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Education and Research, SCPMG, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 16-18—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

October 18-22—**Pacific Dermatologic Association—Annual Meeting.** Reno. Monday-Thursday. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno 89509. (702) 323-2461.

October 19-22—**Electrocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Mark Hopkins Hotel, San Francisco. Monday-Thursday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

October 21—**Endocrine—Third Annual Symposium.** The Hospital of the Good Samaritan at Hyatt Regency, Los Angeles. Wednesday. 7 hrs. $75. Contact: Bonnie VanWaardenburg, Coordinator of Symposia, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 24—**Inflammatory Bowel Disease and Alcoholism—Third Annual Medical Symposium.** El Cajon Valley Hosp. at Hotel del Coronado, Coronado. Saturday. 6 hrs. $50. Contact: Ray Leber, El Cajon Valley Hosp., 1688 E. Main St., El Cajon 92021. (714) 440-1122.

October 24—**Allergy/Immunology.** PMC. Saturday. 6 hrs.

October 24—**Asthma Seminar.** Allergy Fndn. of No. Calif. and Allergy Assn. of No. Calif. at Golden Gateway Holiday Inn, San Francisco. Saturday. 6 hrs. $45. Contact: Betty Miller, MD, c/o Allergy Fndn. of No. Calif., 1449 Drake Ave., Burlingame 94010. (415) 992-0900.

October 24-25—**Diabetes Workshop.** UCSF. Saturday-Sunday.

October 24-31—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

October 25-29—**American College of Chest Physicians.** Hilton Hotel, San Francisco. Sunday-Thursday. 30 hrs. Contact: Dept. of Education, ACCP, 911 Busse Highway, Park Ridge, IL 60068. (312) 698-2200.

October 27—**12th Annual Paul M. Aggeler Memorial Lecture: Von Willebrand's Disease—A Clinical and Molecular Enigma.** UCSF at San Francisco General Hospital Medical Center. Tuesday; 11:30 a.m.-12:30 p.m.

October 28—**Platelet Membrane Function.** UCSF. Wednesday; 10:30 a.m.-12:00

October 28-30—**Neurology for the Internist and Family Physician.** USC at Marriott Hotel, Newport Beach. Wednesday-Friday. 24 hrs. $250.

October 29-31—**Cardiology Update—1981.** American College of Cardiology and UCSF at Quail Lodge, Carmel Valley. Thursday-Saturday. Contact: Registration Sec., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

November 4—**Sudden Death—The Identification and Management of Patients With Malignant Ventricular Dysrhythmias.** Am. Heart Assn., Santa Clara Co. Chap., at LeBaron Hotel, San Jose. Wednesday. 6 hrs. $15, members; $20, nonmembers. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

November 6-8—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Sahara Hotel, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 6-8—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Sheraton, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

November 7—**Neurological Assessment.** PMC. Saturday. 6 hrs.

November 11—**Acid Base Disorders.** LLU. Wednesday.

November 14—**Clinics in Medicine—Nephrology/Hypertension.** PMC. Saturday. 3 hrs. $40.

November 14—**Modern Drug Management of Common Pulmonary Diseases.** UCSF at Fresno. Saturday. Contact: Kathleen Wolff, Area Health Education Ctr., 5110 E. Clinton Way, Suite 201, Fresno 93727. (209) 252-1948.

November 16-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** Am. College of Allergists, Sociedad Mexicana de Allergia E Immunologia, Autonoma Univ. of Baja and UCSD at San Diego (16-18) and Tijuana (19-20). Monday-Friday. 21 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

(Continued on Page 48)

In serious anaerobic pleuropulmonary infections...

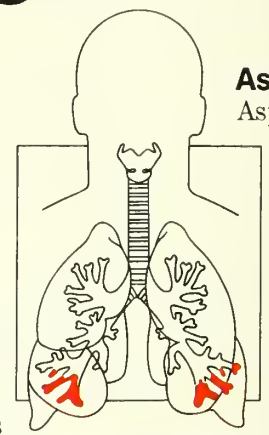
Established clinical effectiveness with broad anaerobic coverage.

More than eight years of clinical experience have established *Cleocin Phosphate*™ (clindamycin phosphate injection) as an effective antibiotic for infections associated with a *broad range* of gram-negative and gram-positive anaerobic pathogens, especially those involving species of *Bacteroides* and *Fusobacterium*, peptococci, and peptostreptococci. (Clostridia are less susceptible than most anaerobes to clindamycin.)

Antibacterial susceptibility

The treatment of many anaerobic pleuropulmonary infections becomes more problematic as patterns of susceptibility change and pathogens unresponsive to standard therapies are encountered more often. Awareness of current anaerobic bacterial susceptibility patterns may thus be a critical factor in selecting an antibiotic for life-threatening infections.[1]

Most pathogens implicated in pleuropulmonary infections are responsive to penicillin G, long considered the drug of choice in such cases.[2] Penicillinase-producing strains of *Bacteroides melaninogenicus* and *Bacteroides oralis*, common isolates in serious pleuropulmonary infections, are being reported with increasing frequency.[3-5] In addition, *Bacteroides fragilis*—typically resistant to penicillin—is involved in an estimated 10% to 20% of such cases.[1]



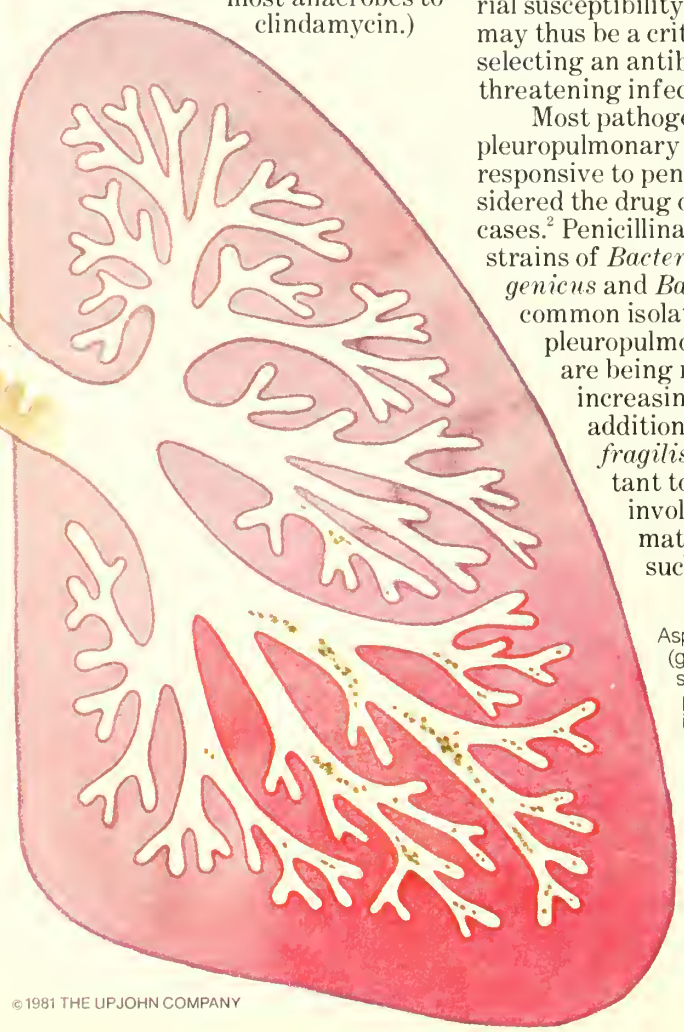
Aspiration pneumonia

Aspiration pneumonia commonly begins with the aspiration of oropharyngeal bacteria when normal gag-reflex and swallowing mechanisms are impeded. Conditions that permit abnormal aspiration and consequent infection include excessive alcohol ingestion, seizure disorders, periodontal disease, cerebrovascular accidents, nasogastric or endotracheal intubation, tracheoesophageal malformations, disorders of the central nervous system, and drug abuse.[2]

Aspiration pneumonia and lung abscess in adults are among the pleuropulmonary infections that have been treated successfully with clindamycin.[6] These infections frequently involve the anaerobes *B. melaninogenicus*, *B. fragilis*, and *Fusobacterium nucleatum*.[5]

Clinical experience

Fifty adult patients with pleuropulmonary infections deemed to be caused by anaerobes were treated with clindamycin either orally or parenterally. Marked improvement or recovery was shown by 46 patients, 3 were considered treatment failures, and 1 had a superinfection.[6]



Aspirated matter (green) and subsequent pulmonary inflammation (red)

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Aspiration pneumonia: Anaerobes commonly recovered include *Bacteroides melaninogenicus, Fusobacterium nucleatum, Peptococcus, Peptostreptococcus* and, in an estimated 10% to 20% of cases, *Bacteroides fragilis.*

Lung abscess: Abscess formation may occur as a complication following aspiration pneumonia. The anaerobic bacteriology reflects that associated with aspiration pneumonia.

B. melaninogenicus blood agar plates

B. melaninogenicus thioglycolate medium

F. nucleatum

In another study of 74 pediatric patients with aspiration pneumonia, bacteriology was established by percutaneous transtracheal aspiration. Anaerobes alone were isolated in 2 cases, aerobes alone in 5, and aerobic and anaerobic organisms in 67 cases. Predominant anaerobic isolates were *B. melaninogenicus, Peptococcus, Peptostreptococcus, Fusobacterium, B. fragilis, Veillonella,* and *B. oralis.* Most isolates were sensitive to penicillin; exceptions were the *B. fragilis* group and some strains of *B. melaninogenicus.*[7]

Initial choice of medication—penicillin G, carbenicillin, or clindamycin, with an adjunctive aminoglycoside when necessary—was based on Gram-stain findings; modifications were made if culture results so indicated. Patients responded to all therapeutic regimens. The authors recommended, however, that in cases of *serious* pleuropulmonary illness, therapy should include an agent active against *B. fragilis* species and strains of *B. melaninogenicus* that might be resistant to penicillin.[7]

Therapeutic conclusions

Penicillin G remains the drug of choice in pleuropulmonary infections. Certain anaerobes resistant to penicillin G have been increasingly identified in *serious* pleuropulmonary infections. In such cases—and in infections where the presence of penicillin-resistant anaerobic pathogens cannot be ruled out—an agent such as *Cleocin Phosphate*, which has proven activity against *Bacteroides* species and most other anaerobes, should be considered.

If significant diarrhea or colitis occurs during therapy, this antibiotic should be discontinued (see WARNING box). A summary of prescribing information for *Cleocin Phosphate*—used in the treatment of serious infections due to anaerobic pathogens—can be found on the following page.

References: 1. Finegold SM: Antimicrobial therapy of anaerobic infections: A status report. *Hosp Pract,* October 1979, pp 71-81. **2.** Bartlett JG: Anaerobic pneumonitis: More common than suspected. *J Respir Dis,* February 1980, pp 46-55. **3.** Hackman AS, Wilkins TD: Influence of penicillinase production by strains of *Bacteroides melaninogenicus* and *Bacteroides oralis* on penicillin therapy of an experimental mixed anaerobic infection in mice. *Arch Oral Biol* 21:385-389, 1976. **4.** Salyers AA, Wong J, Wilkins TD: Beta-lactamase activity in strains of *Bacteroides melaninogenicus* and *Bacteroides oralis. Antimicrob Agents Chemother* 11(1):142-146, 1977. **5.** Bartlett JG, Gorbach SL, Finegold SM: The bacteriology of aspiration pneumonia. *Am J Med* 56:202-207, 1974. **6.** Kapila R, et al: Evaluation of clindamycin and other antibiotics in the treatment of anaerobic bacterial infections of the lung. *J Infect Dis* 135(suppl):S58-S64, 1977. **7.** Brook I, Finegold SM: Bacteriology of aspiration pneumonia in children. *Pediatrics* 65(6):1115-1120, 1980.

In serious anaerobic pleuropulmonary infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)

FOR INTRAMUSCULAR AND INTRAVENOUS USE

Upjohn

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE

WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the Indications section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

Each ml contains:

clindamycin phosphate equivalent to	150 mg clindamycin
disodium edetate	0.5 mg
benzyl alcohol	9.45 mg

When necessary, pH is adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis, and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy. Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *C. difficile*. The usual adult dosage is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis, and in atopic individuals.

Do not inject intravenously undiluted as a bolus; infuse over at least 10-60 minutes as directed in package insert. Indicated surgical procedures should be performed in conjunction with antibiotic therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use of clindamycin may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfections occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting, and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. *Musculoskeletal:* Rare instances of polyarthritis have been reported.

How Supplied: Available as sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription. B-9-S

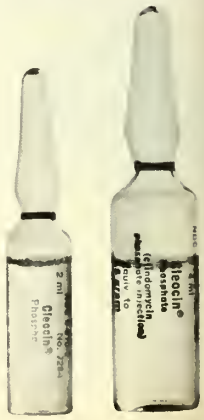
The Upjohn Manufacturing Company
Barceloneta, Puerto Rico 00617

Upjohn

In serious anaerobic pleuropulmonary infections...

Cleocin Phosphate™ STERILE SOLUTION

(clindamycin phosphate injection, USP)
FOR INTRAMUSCULAR AND INTRAVENOUS USE



J-8742

RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract

CONTRAINDICATIONS

None known

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50. The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested)

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless
Protect from strong light
Store at room temperature (50° to 86°F) (15° to 30°C)
Do not autoclave
NDC # 0433-0433-05

DMSO / RIMSO / DMSO

RIMSO®-50
dimethyl sulfoxide
50% w/w aqueous solution

STERILE AND PYROGEN-FREE

50 ml

NDC # 0433-0433-05

FOR FURTHER INFORMATION

DRS. NAME

ADDRESS

CITY STATE ZIP

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1847 West 2300 South
Salt Lake City, Utah 84119

Toll-Free (800) 453-8432

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- Vail OB/GYN Conference Marriott's Mark Resort, Vail
- Vail Psychiatry Conference Lion Square Lodge, Vail
- Vail Geriatric Medicine Conference The Lodge at Vail

February 20-27, 1982
- Aspen Radiology Conference Aspen Institute for Humanistic Studies
- Vail Pathology Conference Kiandra Lodge, Vail
- Community Pharmacy Practice Seminar Enzian Lodge, Vail

February 27-March 6, 1982
- Vail Cancer Treatment Conference Kiandra Lodge, Vail
- Vail Sports Medicine Conference Lion Square Lodge, Vail

March 6-13, 1982
- Vail Family Practice Conference Marriott's Mark Resort, Vail
- Vail General Surgery Conference Lion Square Lodge, Vail
- Vail General Dentistry Conference Kiandra Lodge, Vail

March 13-20, 1982
- Vail Internal Medicine Conference Lion Square Lodge, Vail
- Vail Pediatrics Conference Marriott's Mark Resort, Vail
- Vail Clinical Brain Conference Kiandra Lodge, Vail

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Information/Brochures:
M. BERENSON, MD
4E504 University Medical Center
Salt Lake City, UT 84132
(801) 581-3581

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Four practical reasons to prescribe Ativan® (lorazepam) Ⓒ IV for Anxiety*

1 No interaction with more than 300 drugs†

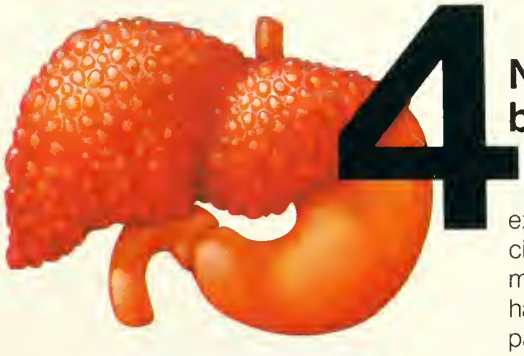
In clinical studies, Ativan was given concomitantly with hundreds of medications, including gastrointestinal and cardiovascular, with no reported interactions. Whereas the interaction of diazepam and cimetidine has been shown to cause increased sedation in patients taking both drugs, the clearance of Ativan is not delayed by Tagamet.‡

2 Lets most patients stay active

Long-acting benzodiazepines have long-acting metabolites with activity which can produce excessive accumulation that may lead to unwanted sedation. Ativan® has no active metabolites, reaches steady state in 2 to 3 days and usually does not cause oversedation. Also, the shorter half-life of Ativan is consistent with b.i.d. dosage, so drug hangover is seldom a problem the next morning.

3 Not appreciably affected by aging

Unlike the long-acting benzodiazepines—diazepam Ⓒ IV, chlordiazepoxide Ⓒ IV, clorazepate Ⓒ IV and prazepam Ⓒ IV—the metabolism and clearance of Ativan are not appreciably affected by the aging process.



4 Not significantly affected by liver dysfunction

Ativan® is metabolized in one simple step to an inactive glucuronide; its absorption and excretion are not significantly altered by cirrhosis or hepatitis. By contrast, the metabolism of diazepam and chlordiazepoxide has been reported to be significantly altered in patients with liver dysfunction.

See important information on following page.

*Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

†All benzodiazepines, however, produce additive effects when given with CNS depressants, such as barbiturates or alcohol.

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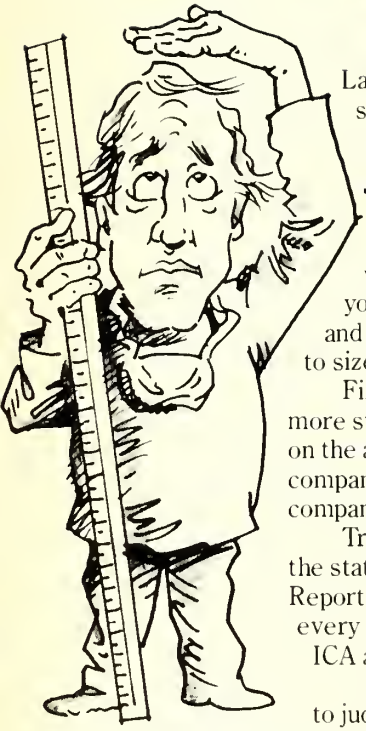

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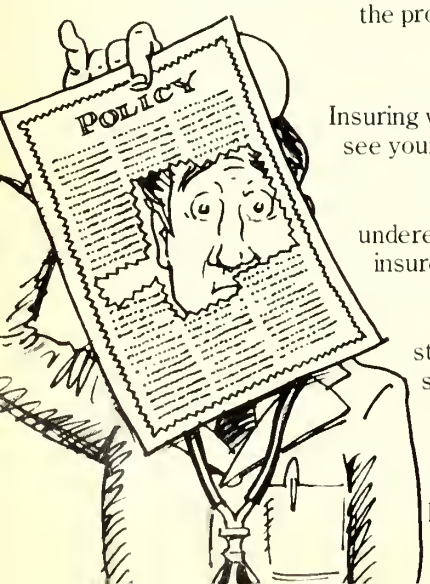

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But don't judge a policy by rates alone.

HOW RENEWING THE VERY SAME POLICY COULD BE GIVING YOU VERY DIFFERENT BENEFITS.

Do your rates stay the same while your benefits shrink? At some companies one or two word

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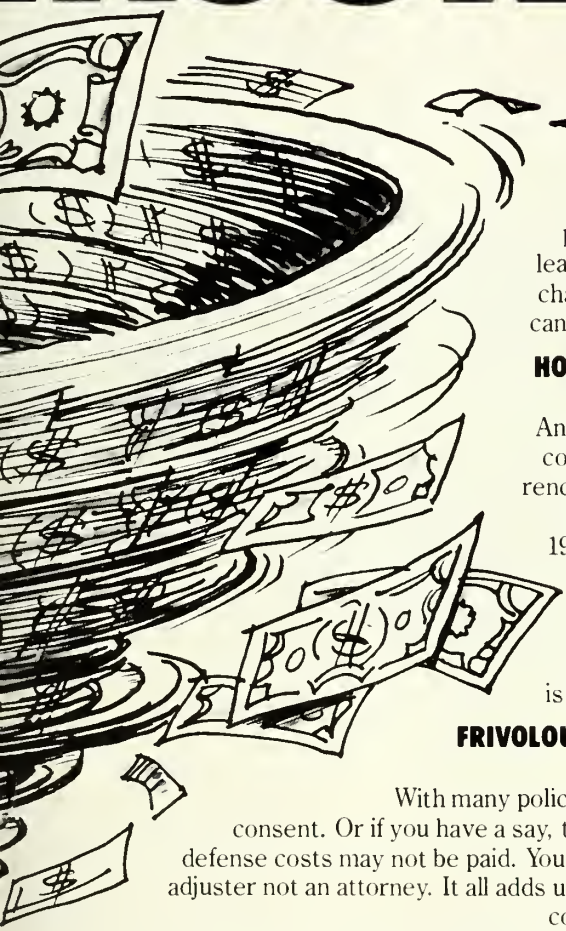
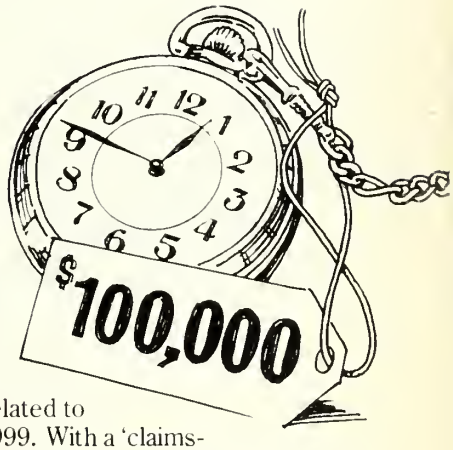


changes each year can keep a policy profitable for them but can leave you increasingly vulnerable. Like changing the consent clause, so a claim can be settled without your consent.



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Another change companies make that can cost you plenty is to switch your 'occurrence-form' policy to a 'claims-made' one. With an 'occurrence-form' policy in say 1979, you're always insured for claims related to that year. Even if a claim is made in 1999. With a 'claims-made' policy coverage expires completely if you fail to renew. To keep coverage after retirement you may have to pay an exorbitant fee set by your company and years of inflation. And the limited coverage it buys you is all you have to cover your entire career.

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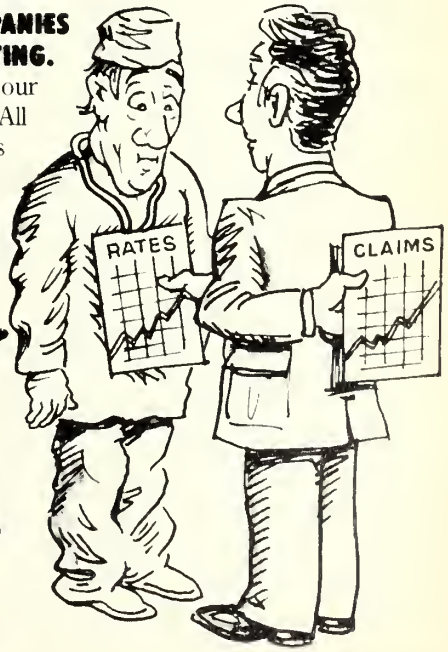
At ICA policies are designed to protect you. Tough, professional handling of claims guards your reputation and helps keep costs down. Ours and yours. At ICA we can offer what others can not. Because we are a doctor and attorney owned company that specializes solely in professional liability insurance. Our background and dedication to this one field have allowed us to both know its needs and know how to meet them.



For more facts, contact: Insurance Corporation of America, ICA Center, 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2615. In Texas 1-800-392-9702. (Check for availability in your state.)

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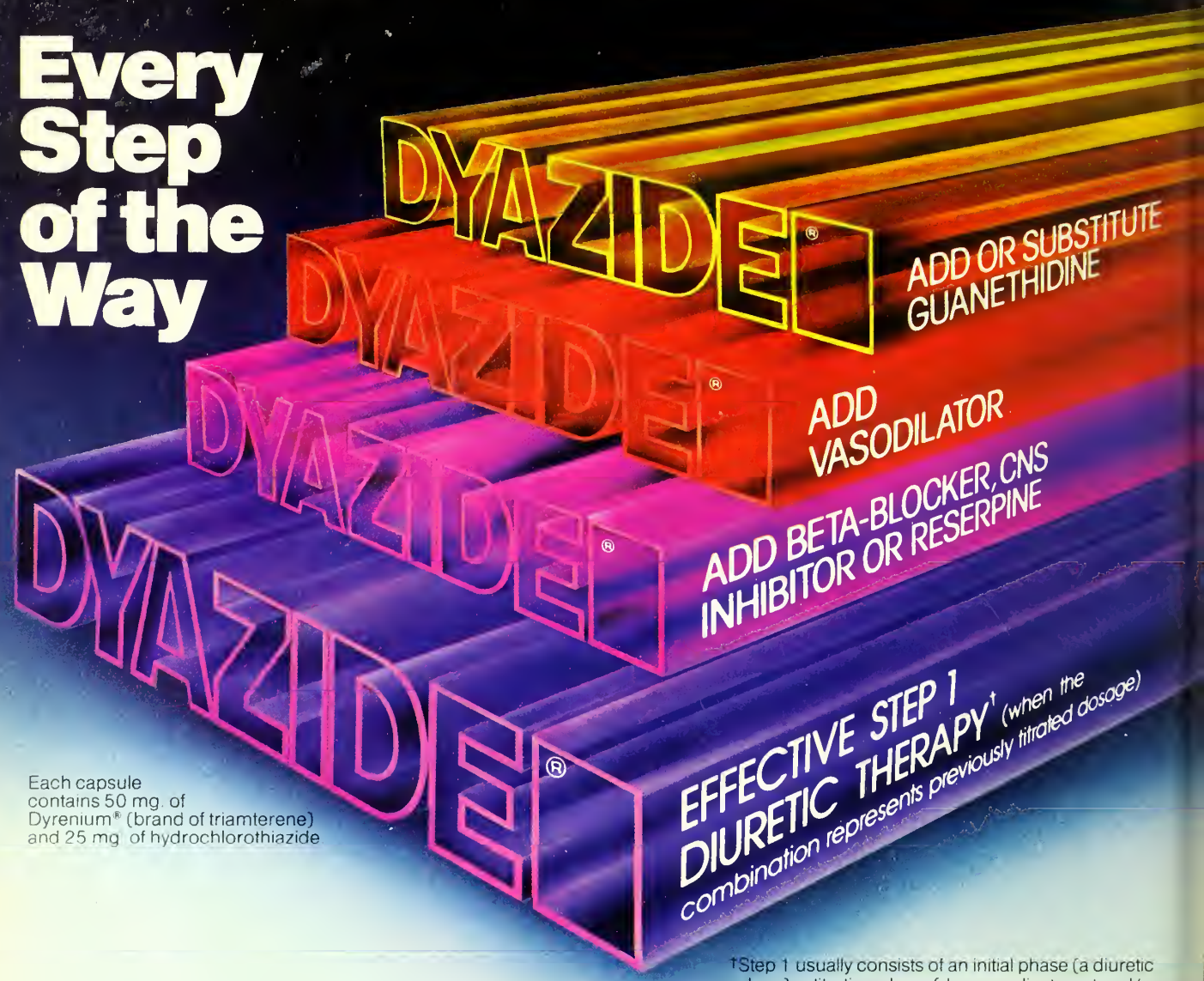

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently, both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: **Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

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THE WESTERN
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Refer to: Borson S, Katon W: Chronic anorexia nervosa: Medical mimic. West J Med 135:257-265, Oct 1981

Chronic Anorexia Nervosa: Medical Mimic

SOO BORSON, MD, *and* WAYNE KATON, MD, *Seattle*

While anorexia nervosa is typically construed as an acute, dramatic disorder of younger women, long-term follow-up studies indicate that morbidity is chronic or relapsing in 30 percent to 50 percent of cases and sometimes leads to death. In older patients or those with atypical clinical features or obscure complications, chronic starvation may mimic other diseases, and rigid adherence to current diagnostic criteria may impede recognition and appropriate treatment. Anorexia nervosa should be viewed as a spectrum of disorders, with varying courses and presentations, in order that clinicians in nonpsychiatric settings may be equipped to provide adequate care of patients with this complex psychosomatic disease.

THE RECOGNITION of classic anorexia nervosa presents no special problems to internists, family practitioners or pediatricians. The patient is usually a young woman brought to the doctor at the behest of her parents; she has menstrual irregularities and is considerably underweight but asserts that she is fat or morbidly in danger of becoming so. She ignores or disputes the doctor's and her parents' pleas to gain weight, denies the dangers of her malnutrition, and occupies herself with feeding others, thinking about food and compulsively regulating her diet. Food refusal is the essential mechanism behind her progressive loss of weight. In the atypical patient, on the other hand, who is older, has a less severe or chronic relapsing course, presents unusual clinical features, or whose loss of weight is no longer the subject of public complaint by family members, complications of chronic starvation may develop, which mimic other diseases, confound the diagnosis, and delay appropriate treatment. This paper describes a chronic form of anorexia nervosa that occurs in up to a third of patients and discusses the diversity of medical presentations in this group in order to contribute to clinicians' understanding of eating disorders as they appear outside the psychiatrist's office.

From the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle.

Submitted, revised, May 1, 1981.

Reprint requests to: Soo Borson, MD, Department of Psychiatry (116B), Veterans Administration Medical Center, 4435 Beacon Ave. South, Seattle, WA 98104.

Diagnosis of Anorexia Nervosa

Anorexia nervosa is the paradigmatic psychosomatic disease: both characteristic psychological and physical abnormalities are required for diagnosis, and both must be addressed for treatment to be successful. Feighner and co-workers[1] have defined the diagnostic criteria now in wide use; these are presented in detail in Table 1. "Anorexia" is a misnomer, as the typical patient with early anorexia nervosa is not anorexic at all; she

TABLE 1.—*Diagnostic Criteria Used to Identify Cases of Anorexia Nervosa**

Onset by age 25
Anorexia with a weight loss of 25 percent or more of body weight
Distorted attitude toward food, eating and weight that overrides hunger, threats and reassurances, and is manifested by the following:
Denial of illness with failure to appreciate nutritional needs
Pleasure in the loss of weight and avoidance of food
Disturbance in desired body image (that is, extreme thinness is preferred)
Unusual handling of food
No medical illness to account for loss of weight
No other known psychiatric disorder
Presence of two of the following:
Amenorrhea
Lanugo
Bradycardia
Overactivity
Episodes of bulimia
Vomiting (may be self-induced)

*From Feighner et al.[1]

refuses to eat. She experiences hunger but is gratified by her ability to repudiate it.

Bruch,[2] Palazzoli,[3] and Minuchin and colleagues[4] stress distinctive patterns of family interaction among anorexic patients and their relatives and emphasize the central significance of food as a symbolic weapon in an intense struggle for power and autonomy between those with anorexia and their parents. Dysfunctional family interactions have been described by several authors.[2,4-6] A teenager with acute anorexia may complain to her physician about her overprotective or domineering mother who will not let her date, leave home, have a pet or choose her own clothes. However, older patients, for whom issues of self-control, autonomy and emancipation are no longer part of a culturally sanctioned and age-appropriate developmental crisis, have not been previously as well described in the literature. Persons with anorexia of all ages manifest multiple defects in self-regulation: they respond to the demands and needs of others at the expense of themselves; they feel a pervasive sense of ineffectiveness and are unable to label and discriminate emotions and bodily needs. They often respond to perceived authority figures with docile overcompliance. On the surface, these patients frequently appear unusually thoughtful of others, altruistic and achievement-motivated. Bruch argues that these psychological characteristics are decisive in the pathogenesis and outcome of anorexia nervosa and should not be eliminated from the requirement for diagnosis; as yet this point of view is not reflected in the modern diagnostic criteria against which patients' presentations are matched. (H. Bruch, MD: Unpublished comments on paper presented by D. M. Schwartz, PhD, at the annual meeting of the American Psychiatric Association, Chicago, 1979.) We believe that these same characteristics, displayed in the medical setting, contribute to physicians' failure to recognize the correct diagnosis. What follows is the application of inappropriate diagnostic methods and neglect of referral for definitive psychological treatment until the dysfunctional behavior patterns and physiological consequences of starvation become hopelessly entrenched.

While strict phenomenological criteria are helpful in the differential diagnosis of young underweight patients who are coming to medical attention for the first time, their emphasis on age of onset and quantity of weight lost can be misleading in several clinical situations. The first is where age and the accretion of medical diagnoses dominate the clinician's perceptions of an older, underweight woman. The diagnosis of anorexia nervosa is unlikely to be considered: the patient is "too old" or "too sick" for anorexia. The second occurs when physical symptoms, such as abdominal pain, weakness or fatigue are prominent in the patient's complaint. Finally, a patient who comes for dietary advice and seems to have certain unusual ideas about food—but is not currently underweight—may be seen by her physician as neurotic or oddly overconcerned but not as being at risk for anorexia nervosa.

In the following sections we review the current literature on chronicity in anorexia nervosa, on its medical presentations, and on the physiological abnormalities that accompany chronic starvation. We then report two illustrative cases and outline a conceptual approach with special relevance for primary care.

Incidence of Chronic and Atypical Forms of Anorexia Nervosa

Beck and Brochner-Mortensen,[7] in their 1954 study of 28 patients with anorexia who were admitted to a medical service, with follow-up ranging from five months to 23 years after index admission, found 4 patients with symptoms lasting more than 8 years. More than half of the 38 patients in a study by Kay and Leigh[8] continued to show definitive signs and symptoms of anorexia nervosa at follow-up, 2 to 19 years after onset.

In a study by Cremerius,[9] 6 of 13 patients had continued a chronic course of undernutrition when assessed 15 to 18 years after onset of the disease. In Theander's study[10] of 94 anorexic patients, about a third ran chronic courses of six years or more. Five of these patients were diagnosed in their 20's and 30's but were found to have had an adolescent episode 6 to 18 years before.[10] In the study by Hsu and colleagues[5] of 100 patients, 50 had persistent anorexia nervosa or otherwise unsatisfactory outcome at follow-up four to six years after diagnosis. Other investigators confirm these trends.[6]

Bruch[2] described a group of 20 chronically ill patients seen 6 to 19 years after onset. Three had died of complications of starvation and four had become chronically psychotic. Five had chronic anorexia nervosa; 11, though maintaining normal weight, were obsessively preoccupied with weight, lived very restricted lives and were considered at risk for recurrent episodes of clinical anorexia nervosa.[2] Loeb[11] reported two anorexic patients first seen at relatively advanced ages (32 and 52); both had had adolescent episodes of classic anorexia, but neither had received medical consultation about this disorder.

Schwartz and co-workers[12] combined 12 published studies of course and outcome in patients with anorexia nervosa, representing more than 600 patients. Using weight, symptoms regarding eating and mortality as outcome measures, they found that 56 percent of patients experienced continuing morbidity related to anorexia nervosa or had died. Eighteen percent had clearcut anorexia nervosa at follow-up. Thirty-one percent were no longer frankly anorexic but had continuing weight fluctuations, were overweight, or had persistent eating disturbances. Six percent had died of complications of starvation. It is clear that anorexia nervosa is not only an acute disorder of young women but one that may persist into mid and late life in classic as well as altered or attenuated forms.

The medical presentations of chronic anorexia nervosa are poorly delineated in the literature and are either omitted from tabulation in the larger case studies or described in smaller case reports as unusual features of the disease. Gynecologists are often the first physicians consulted, because of amenorrhea, which is a part of the anorexic syndrome. We found only one detailed report[7] of a series of patients admitted for treatment to a medical service. The most common presentation was of a gastrointestinal syndrome. Of 36 patients, 15 complained of varying combinations of symptoms: epigastric fullness, nausea, abdominal pain, dysphagia, vomiting, dyspepsia and "upper abdominal colic." The next most frequent chief complaint was of weakness, in 13 patients. This symptom is particularly notable because of the prevailing view among physicians, derived from classic descriptions of the disease, that patients with anorexias are energetic and hyperactive. Though physical activity out of keeping with the severity of malnutrition is indeed a hallmark of the disease, it may be absent in a significant proportion of patients even before inanition develops.[2]

Physiological Abnormalities in Simple Starvation and Anorexia Nervosa

The Biology of Human Starvation by Keys and his colleagues[13] collates a vast experience with human starvation. The authors reviewed the world literature on naturally occurring starvation and reported in detail their own studies of experimental semistarvation in volunteers. Later studies have elaborated but not substantively altered their findings. Similarly, the classic clinical findings in anorexia nervosa have been given a firm footing in modern biochemistry and physiology by refinements of laboratory measurement. By and large, the abnormalities associated with starvation imposed by food shortage or by voluntary experiment appear indistinguishable from those of self-imposed starvation. Table 2 summarizes these. Of particular interest is the occurrence of a psychiatric syndrome, characterized by intense preoccupation with food, peculiar eating habits, abnormal regulation of intake when food is available, hypochondriasis, irritability and depression, in previously normal young men subjected to experimental semistarvation during six months.[13] These are the same clinical psychiatric abnormalities most commonly described for those with anorexia. In the experimental subjects, the cognitive and emotional concomitants of starvation frequently outlasted the starved state; in some persons, eating behavior and attitudes toward food remained abnormal for months after restoration of normal weight—a phenomenon generally thought to occur only in anorexia nervosa.

The pathophysiology of starvation of any cause may mimic several classic diseases or suggest rare and puzzling syndromes if the full clinical picture and the patient's social context are not appreci-

TABLE 2.—*Abnormalities in Simple Starvation and Anorexia Nervosa*

Functional System and Reference Numbers	*History and Symptoms*	*Findings*
Endocrine-metabolic (4,13-17,22,23)	Cold intolerance*	Normal thyroid gland*,†
		Normal TSH
		Decreased T_3† and BMR*
		Increased serum cholesterol
	Amenorrhea or menstrual irregularity*,†	Normal pelvic examination results
	Disinterest in sex (male and female)*,†	Decreased FSH, LH, response to LHRH
		Decreased estrogen production‡
	Weakness*	Increased cortisol and urine free cortisol
	"Hypoglycemia"*	ACTH normal or increased
	Lightheadedness*	Decreased suppressibility by dexamethasone
		Decreased serum insulin and RBC insulin binding
		GTT flat or diabetic
		Salt and water balance may be abnormal
	Large urine volumes§	Deficient ADH‖
		Normal or increased serum GH
		Decreased GH response to glucagon, propranolol, TRH, and levodopa
		Decreased, increased or normal serum Ca^{++}, PTH*,†
Gastrointestinal (13,24-27)	Vague abdominal complaints*,†	Atrophy of gut and associated structures (pancreas, gall bladder, liver)
	Multiple food intolerances†	
	Vomiting,*,‖ diarrhea,*,† constipation* (may be severe)	Mucosal atrophy*
		Motility disturbance; functional obstruction*,†
		Decreased gastric HCl and fluid secretion
		Malabsorption states with refeeding ("gut overload"); no specific pattern*
		Ulceration—anywhere in GI tract*
		Gut rupture*
Musculoskeletal (13)	Myalgia*	Diffuse muscle atrophy*,†
	Bone pain, fractures*	Osteopathies*:osteoporosis, osteomalacia
Hematologic (13,28-30)	Nonspecific: fatigue,* "washed out," decreased energy	Anemias*,† esp. iron deficiency
		Leukopenia†
	Bleeding (rare)	Thrombocytopenia
		Bone marrow hypoplasia*,†
		RBC abnormalities: acanthocytosis
Cutaneous (13,23)	Easy bruising*	Atrophic dry, rough, scaly skin*
	Color change (pallor,* yellow cast)	Carotenemia
		Abnormal brown pigmentation*
Cardiovascular (13,23)	Specific complaints unusual	Bradycardia
		Hypotension*
		Arrhythmias (with electrolyte imbalance)
		Cardiomyopathy and congestive heart failure* (terminal)
Cognitive (13)	Impairment of memory and concentration*	Transient delirium* (with electrolyte abnormalities; abnormal EEG confirms)
	Confusional states*	
Behavioral (1-3,9,11,14)	Emotional lability	MMPI: "Starvation neurosis"* (increased depression, hypochondriasis, and hysteria scores; lesser increases in schizophrenia, psychasthenia scores)
	Depression*,†	
	Social withdrawal*,†	
	High bodily concern*,†	
	Hyperactivity preceding apathy*,†	Dissociation of thought and feeling*,†
	Preoccupation with food*,†	Varying affective disturbances†
	Eating rituals†	Psychosis may occur
	Bizarre food habits†	
	Dreams about food	
	Periodic gorging	
Miscellaneous (13)	Varies with clinical condition	Increased ESR (mild)*
		Decreased serum albumin*
		Changes in serum globulins*

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; BMR = basal metabolic rate; Ca = calcium; EEG = electroencephalogram; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; GH = growth hormone; GI = gastrointestinal; GTT = glucose tolerance test; HCl = hydrochloric acid; LH = luteinizing hormone; LHRH = luteinizing hormone releasing hormone; MMPI = Minnesota Multiphasic Personality Inventory; PTH = parathyroid hormone; RBC = red blood cell; T_3 = triiodothyronine; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

*Our case 2 } In addition to cited reports in literature.
†Our case 1 }
‡Changes in testosterone secretion in males have not been studied.
§Rare in simple starvation; may be concealed in anorexia nervosa.
‖Not studied in simple starvation.

ated. Skin changes, bradycardia, increased levels of serum carotene, hypometabolism and decreased levels of serum triiodothyronine (T_3) suggest primary hypothyroidism; bone changes with associated signs of abnormal calcium metabolism simulate primary parathyroid disease. Pigmentary abnormalities, hypotension and weakness hint at Addison's disease, while elevated levels of serum cortisol and emotional changes suggest Cushing's syndrome. Functional bowel disturbances are extremely common and the friable gut of the chronically starved may give rise to sepsis or to obscure, recurrent febrile illness that eludes exact diagnosis. The clinical presentations of starvation display great diversity and are shaped by numerous influences. Among these are the duration, type and amount of food restriction, the kinds of foods eaten during starvation, the person's preexisting health status and special nutritional needs (as in adolescence or during pregnancy), and coexisting infections or other illnesses.[13]

Findings in simple starvation and anorexia nervosa also differ in several ways. In malnourished persons who are not anorexic, normalization of the hypothalamic-pituitary-adrenal loop occurs promptly with nutritional repletion.[15] In contrast, patients with anorexia nervosa often continue to show signs of hypothalamic dysfunction even after restoration of body weight; these include defects in water conservation and thermoregulation,[16] menstrual abnormality, and several abnormal responses of pituitary hormones to hypothalamic-releasing factors.[4,15,17] These findings suggest that disturbed hypothalamic function may be an early and sensitive reflection of the emotional disturbance in this disorder, though there is substantial variation in the degree and persistence of these abnormalities, and studies adequately controlled for duration and severity of starvation are few. Of interest is the mounting evidence of hypothalamic-pituitary dysfunction in various stress states[18] and in some patients with primary depressive disorders.[19,20] A specific pathogenetic role for the hypothalamus in anorexia nervosa has not been demonstrated, and, from a clinical standpoint, persistent food refusal in the pursuit of thinness remains the core and primary abnormality in this disease. The protean medical manifestations and the associated chemical and pathological findings that result from persistence of this behavior over time, should alert us to the existence of this underlying mechanism—not be taken for the disease itself. The following two case reports illustrate some consequences of such confusion.

Reports of Cases

CASE 1. A 33-year-old woman and mother of five children was referred to the University of Washington Hospital Medical Service in Seattle, for evaluation of abdominal pain, anorexia, weight loss and diarrhea. She had been ill on and off for ten years, with abdominal pain, occasional nausea and vomiting, anorexia and diarrhea. These symptoms had worsened considerably in the last six months and the patient responded by sharply limiting her diet to fresh boiled vegetables, fish, yogurt, soft drinks and salads. She presented an elaborate list of foods that increased her nausea or diarrhea.

The patient had had two extensive medical workups, which showed mild anemia, leukopenia, hypoproliferative bone marrow, a slightly low T_3 and lactose intolerance, and failed to explain her symptoms. Psychiatric consultation was requested to further investigate her illness, while more extensive medical workup was being contemplated.

Psychiatric examination showed a perfectly groomed, cachectic young woman, with an insistently cheerful but brittle facade. While accepting psychiatric consultation, she maintained that her life was entirely satisfactory except for her now chronic illness; she assumed that the doctors would eventually find the cause and cure for her progressively disabling gastrointestinal disease. The patient reported a marriage untroubled by any but "the usual problems everyone has." A convert from Judaism to her husband's faith, she expressed great satisfaction in raising a close, Catholic family. She denied hostile feeling toward her husband though they were clearly evident as she spoke. She admitted to a mild depression, however, and had withdrawn from her usual active schedule during the last year. She had decreased her intake to less than 1,000 calories per day, had lost 25 pounds and was jogging up to 12 miles a day; her current weight, 84 pounds, was "ideal." With bland emotion she reported the early death of her mother, which left her in the care of a cold, demanding father whom she felt she could never please. Her father rigidly controlled the family, allowing little expression of individuality by the children. At 20 she married her husband, a warm and loving man who courted her.

The interview with her husband painted a dramatically different picture. Dissatisfied with the

marriage for several years, he had confessed a year earlier to an affair with a mutual close friend. He had considered leaving his wife, but conflicts between his principles and impulses had prevented what he viewed as desertion. Since then, his wife had refused sex; their lives became increasingly dominated by her illness and meticulous, time-consuming attention to diet. He felt blackmailed into relinquishing emotional as well as physical intimacy and believed his wife was punishing him with her illness and withdrawal. He was eager for psychotherapeutic help to resolve his persistent turmoil and tension.

The patient had had symptoms of gastrointestinal illness associated with emotional stress for ten years before the onset of this severe episode of typical anorexia nervosa. She minimized or denied painful and negatively toned emotions, substituting somatic symptoms in their place. She thereby avoided overt clashes with her husband, who felt unable to leave a sick wife or to insist on changes in the marriage. The diagnosis of anorexia nervosa adequately accounts for all of her physical symptoms and the laboratory findings. We recommended individual and marital therapy for our patient and her husband, with attention to improving her nutritional state and altering the marital dynamics that precipitated her illness. The patient refused psychiatric follow-up, opting to spend a month at a Catholic monastery to rest and regain her strength. She has remained chronically underweight, has idiosyncratic dietary habits and continues to have gastrointestinal symptoms during periods of stress.

Case 2. A 56-year-old woman was admitted to the University of Washington Hospital Medical Service because of weakness, tachycardia and dyspnea after a protracted gastrointestinal illness with vomiting and diarrhea. She had lost eight pounds in six weeks and had become bedfast, weighing 75 pounds on admission. Because of electrolyte abnormalities, unstable blood pressure and weakness, two medical workups were done, each for adrenal insufficiency and Cushing's syndrome—always with negative results. Back pain, weakness, malnutrition and slight elevations of serum calcium levels had prompted evaluation for parathyroid disease. X-ray studies had confirmed the presence of diffuse osteoporosis, and serum parathormone determinations were variably normal to borderline high; because of persistent debility, attributed by her physicians to subtle hyperparathyroidism, parathyroidectomy was done. No adenoma (and only minimal hyperplasia) was found. The operation, however, produced permanent symptomatic hypothyroidism and hypoparathyroidism.

Though she took her thyroid supplements reliably, she skimped on the prescribed calcium and vitamin D and had several episodes of tetany and hypocalcemic delirium, which required hospital care. Two years earlier she had barely escaped death from catastrophic esophageal rupture and septic mediastinitis. Throughout her course, malnutrition, anemia, electrolyte abnormalities and a plethora of vague symptoms had been recorded. She had been obscurely ill for ten years, her course marked by numerous hospital admissions for illnesses much like this one; intensive workups had shown a panoply of abnormal but constantly changing laboratory tests.

Physical examination showed a vivacious but cachectic woman with mild congestive heart failure, dry, flaky skin and striking brown pigmentation over the back and chest. Laboratory tests showed iron deficiency anemia and mild hypocalcemia. After successful diuresis, her weight was 25 percent below the ideal for her height and age, though she preferred a slightly higher weight (80 pounds). Despite oral caloric supplements her average daily intake was less than 200 calories per day. An astute house officer wondered if she might have anorexia nervosa and requested psychiatric consultation to explore her refusal to eat.

The consulting psychiatrist found a friendly, bright, outgoing woman of considerable charm. She was "bored" with the badgering of her doctors and husband to gain weight and viewed the psychiatric consultation as merely another effort in that direction. Careful history showed that an episode of classic anorexia nervosa in adolescence had been diagnosed as hypothyroidism and remitted spontaneously in her early 20's. She had married, converted from a Protestant sect to Catholicism (her husband's religion) and had borne six children in the ensuing 15 years. Weight and menstrual function fluctuated substantially between pregnancies. Following the birth of her last child, she began to lose weight steadily, ceased menstruating and worried constantly about being too fat despite her husband's begging her to eat more. All coital activity ceased.

The patient said that her greatest pleasure in life had been providing her children with warmth, love and plenty of delicious food, which she would prepare with great concentration but not eat her-

self. Her physical health and stamina began to decline as her children left home one by one. Despite vigorous daily exercise "to keep up her strength," she was forced to spend increasing periods in bed. She had experienced intermittent depressive symptoms for years; these had recently intensified. With sleep disturbance characterized by frequent awakenings and early morning insomnia, fatigue and feelings of despair which regularly improved late in the day, a pervasive loss of pleasure in her usual activities, a sense of failing concentration and belief that she had somehow brought all this on herself, she easily met the strict criteria for a major depressive episode, though she failed to demonstrate depressed affect. She was incongruously cheerful, and her talk was witty and somewhat bawdy. A diagnosis of severe chronic anorexia nervosa with secondary depression was made, and the patient was transferred to the psychiatric service for intensive treatment.

Behavioral and family therapy techniques, now standard in the psychiatric treatment of anorexia, were instituted; after a stormy two weeks, rapid weight gain began with a daily food intake as high as 2,800 calories; at three weeks she had gained ten pounds. She and her husband began to explore their long-term marital estrangement and her defensive use of cachexia to avoid sexual pressure. When she verbalized her long-suppressed anger at him for his violent temper, physical abusiveness and emotional neglect, nausea and difficulty swallowing food developed. The intensity of her complaints interrupted treatment for medical workup, but a barium swallow showed no lesion responsible for her symptoms. Over the ensuing week, a severe barium impaction developed, followed by fever and hematemesis, and the patient was transferred to the medical service for more vigorous management. Femoral artery thrombosis followed, then multiple colonic perforations and septic peritonitis. At surgery, complete repair was obviously impossible; the entire bowel was paper thin and was studded with necrotic patches. Despite aggressive medical and surgical management, she died a week later in massive vascular collapse.

In this patient, the menopausal state and multiple childbirths without nutritional repletion between pregnancies doubtless accelerated the tissue breakdown caused by her self-imposed chronic starvation. Lack of recognition by her physicians of her chronic anorexia nervosa led to numerous unproductive workups and the failure of nutritional supplements and advice. The focus on physical symptoms protected her from her own painful psychic conflicts and from her husband's overbearing demands. The same symptoms, intensified with emotional turmoil in psychotherapy, detoured a promising start on the resolution of these problems back into the medical domain and, ultimately, led to her death from the complications of chronic starvation and overly aggressive refeeding.

Discussion of Cases

For both patients, manipulation of food intake and symptoms of physical illness served as the tools by which they maintained tenuous psychic and marital equilibrium. Their emaciation and illness made refusal of sexual contact and emotional intimacy acceptable. Dysfunctional mechanisms for coping with emotional distress were clearly shown in formal psychological testing and psychiatric interviews, although charm and social competence concealed these deficits from others. Both patients demonstrated serious deficiencies in their sense of personal identity and capacity for healthy self-assertion. Their coping styles hinged on denial, minimization and somatization of affect and interpersonal conflict. Their physicians, by pursuit of repeated, nondefinitive endocrine, gastrointestinal (GI) and hematological investigations helped each of them legitimize and rigidify a medical sick role.

Many of the physiological effects of chronic starvation were evident in both cases: anemia, hypoproliferative bone marrow, leukopenia, decreased triiodothyronine, thyroxine and luteinizing hormone levels, abnormal gastrointestinal motility, diarrhea and amenorrhea in case 1, and low basal metabolism rate, cold intolerance, abnormal calcium metabolism, osteoporosis, serum protein abnormalities, electroencephalographic abnormalities, anemia, altered skin texture and pigmentation, GI mucosal atrophy and large bowel ulceration and rupture in case 2. In case 2, ten years of symptoms that suggested a polyendocrine syndrome had prompted extensive and repeated evaluations without definitive results. The parathyroidectomy, for a presumptive diagnosis of parathyroid adenoma, led to severe and chronic problems with calcium metabolism because of the patient's refusal to satisfy adequate nutritional needs. At no time during her course was a full differential diagnosis of malnutrition entertained.

What accounts for the failure of numerous physicians who cared for and commented on these

patients to recognize the correct diagnosis? In each case, the age of the patient, the history of childbearing, and the presence of physical and laboratory signs of medical illness not attributed to chronic starvation, were confounding variables. Further, both women were attractive, intelligent, apparently compliant patients with none of the obvious oddities of behavior or feeling that typically accompany major psychiatric disorders. This apparent "normalcy," despite substantial disturbance of self-identity and of capacity for intimate relationship and self-identity, set the stage for progressive disability, numerous unnecessary medical procedures and, ultimately, for our second patient, death. Early recognition of the underlying anorexia nervosa and referral to a skilled psychotherapist may have permitted resolution of the psychopathologic state. At the least, it would have curtailed or prevented the entrenchment of dysfunctional illness behavior and the biomedical nightmare that accompanied it.

Implications and Suggestions for Practitioners

We have illustrated what we believe to be an increasingly prevalent clinical syndrome—chronic anorexia nervosa in adults, presenting with diverse medical complaints. Our patients, like others with anorexia, concealed their dedication to abnormal slimness from their physicians, who entertained increasingly obscure diagnostic possibilities to explain their malnutrition.

Anorexia nervosa is best viewed as a spectrum of disorders, with acute self-starvation in young unmarried women at one end and persistent dietary idiosyncrasies in older patients of normal weight at the other. Palmer[21] has described the latter as the "dietary chaos syndrome," in which patients, often having had frank anorexia at an earlier time, have switched their preoccupation from weight to food and eating; these patients demonstrate any of several kinds of distortion of eating behavior. Periods of conflict and stress are associated with intensification of dysfunctional eating patterns, which prompts these persons to visit a physician with nonspecific systemic symptoms or gastrointestinal complaints. Many of these patients, having recovered normal weight, would have been categorized in the older medical literature as cured anorexics. However, investigators such as Bruch, and others cited earlier, have described the social and psychological disability of many former anorexics that lingers on indefinitely after weight recovery. They stress the indispensability of appropriately informed psychotherapy in the long-term management of these patients. Tube feeding, intravenous hyperalimentation, behavior modification to increase food intake, conjoint treatment of the patient and her intimates, special training in appropriate assertiveness, self-help groups, and individual dynamically oriented psychotherapy all have a place in the treatment of this disorder. Controlled comparisons of the effectiveness of different psychotherapeutic modalities have not yet appeared in the literature. It is likely, however, that no single approach will stand alone as specific for anorexia nervosa.

We suggest that physicians who see patients with obscure systemic or gastrointestinal complaints add to their diagnostic armamentarium this broadened understanding of the anorexia spectrum. We recommend a detailed history of eating patterns, idiosyncrasies in food preference, and food preoccupations in the clinical evaluation of underweight patients with unclear nutritional syndromes or vague constitutional or "psychosomatic" complaints. Patients should be asked what weight they prefer and what weight their spouses, parents, siblings, and children think they should be. Family members should be interviewed to clarify the role that food refusal and somatic symptoms play in the patient's relationships. Patients of normal weight who have clear food preoccupations should be asked what measures they must take to keep themselves from becoming fat and an adolescent episode of typical anorexia nervosa sought. Occasionally, obese patients have histories of anorexia in earlier life. Their obesity in part reflects ongoing conflicts over caring for others, being cared for and being in control, and it may predict unusual recalcitrance to a sought after reducing program. Finally, clinicians do well to bear in mind that in our affluent culture, where food is relatively cheap and readily available in quantity and variety, disturbances in interpersonal and intrapsychic functions have a ready nutritional vehicle for expression—whether by refusal to eat, refusal to limit eating or adoption of bizarre rituals and patterns of food intake unrelated to nutritional need. So informed, he or she is then properly equipped for the subtle diagnostic and therapeutic discriminations required by the patients we have described, and others like them.

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Refer to: Dales LG, Chin J: An outbreak of congenital rubella.
West J Med 135:266-270, Oct 1981

An Outbreak of Congenital Rubella

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A large outbreak of rubella occurred in the San Francisco Bay Area in early 1979. Later that year and in early 1980, 13 cases of confirmed or probable congenital rubella syndrome were reported. Results of a subsequent investigation strongly suggest that these two events were related in a causal manner and do not represent an indirect association based on changes in diagnostic or reporting thoroughness. To prevent such episodes in the future, renewed emphasis must be placed on routine immunization of young children of both sexes, rigorous enforcement of school-entry immunization laws and selective immunization of women of childbearing age.

A LARGE OUTBREAK of rubella occurred in the San Francisco Bay Area counties between February and May of 1979; more than 1,000 cases were reported and serological confirmation was obtained for many. Disease activity was most evident in the cities of San Jose and San Francisco. In 45 percent of reported cases, patients were of high school age or slightly older (15 to 19 years), in 23 percent they were in elementary or intermediate schools, in 17 percent they were adults (20 to 29 years) and in 15 percent they were preschoolers or older adults.

The California Department of Health Services (DHS) was notified of two therapeutic abortions done in May 1979 in pregnant women in whom rubella had developed during the outbreak; in both instances rubella virus was isolated from fetal tissue. Several cases of congenital rubella syndrome (CRS) were reported from the San Francisco Bay Area the following fall and winter. DHS records were reviewed to determine whether the rubella outbreak in the preceding winter and spring had been followed by a real increase in CRS cases.

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Submitted, revised, June 16, 1981.

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Methods

Reporting of rubella cases, including cases of CRS, to health departments is a legal requirement in California. DHS records were reviewed to determine the number of rubella cases reported for the calendar years 1976 through 1979 and the number of reported CRS cases born in the July-June, or *fiscal*, years 1976-1977 through 1979-1980. The July-June interval was chosen for CRS cases because rubella activity generally peaks in the late winter and spring, so that resultant CRS cases would be expected to cluster in the following fall and winter, thus overlapping two calendar years. As a means of identifying laboratory-confirmed cases of CRS that were not reported, records of rubella virus isolations made by the DHS Viral and Rickettsial Disease Laboratory in the years 1976 through 1980 were reviewed. The state laboratory was the only laboratory in Northern California carrying out diagnostic rubella virus isolations during this time. Neither the state laboratory nor any other Northern California laboratory routinely offered diagnostic rubella IgM antibody determinations before 1979. Therefore, laboratory records of rubella IgM antibody determinations were not used as a screening device in order to avoid a

ABBREVIATIONS USED IN TEXT

CRS = congenital rubella syndrome
DHS = Department of Health Services
HI = hemagglutination inhibition (titer)

secular bias in case ascertainment. A third method of searching for unreported cases, screening the state laboratory records for infants who at three months of age or older had rubella hemagglutination-inhibition (HI) titers above and beyond those expected from passive transfer of maternal antibody, was tried and abandoned because it was found to be unproductive. CRS cases discovered were classified as to diagnostic certainty in accordance with the criteria recently published by the Centers for Disease Control.[1]

Results

Reported rubella cases for the calendar years 1976 through 1979 for the five San Francisco Bay Area counties most prominently affected in the 1979 outbreak (Santa Clara, San Mateo, San Francisco, Contra Costa and Alameda) and for the remainder of the state are shown in Figure 1. As can be seen, in the five affected Bay Area counties the number of cases reported in 1979 was approximately six times higher than the numbers reported in each of the three preceding years. For the remainder of the state, no increase was seen in 1979 compared with the three previous years.

Figure 2 shows the number of confirmed or probable CRS cases discovered for the five Bay Area counties and for the rest of the state. Cases are grouped by July-June years, beginning with July 1976. According to the Centers for Disease Control criteria used, a confirmed case is one with defects consistent with CRS and one or both of the following: rubella virus isolated or rubella-specific IgM present. A probable CRS case is one with laboratory data insufficient for confirmation but with any two conditions listed under part 1, or one from part 1 and one from part 2, as follows: (1) cataracts or congenital glaucoma, congenital heart disease, loss of hearing or pigmentary retinopathy and (2) purpura or thrombocytopenia, splenomegaly, onset of jaundice within 24 hours after birth, microcephaly, mental retardation, meningoencephalitis or radiolucent bone disease.

As can be seen, there was a sharp increase in cases of CRS from the San Francisco Bay Area counties for the 1979-1980 year. Of these 13 cases, 11 were in the confirmed category (Table 1), and all 13 infants were born between July 1979 and February 1980, which fits well temporally with the prior rubella outbreak in the late winter of 1978 and spring of 1979. For 11 of the infants, the mothers' ages at delivery were available. The range was 17 to 34 years (mean of 21.4 years). In 70 percent of the women, a history of rash illness or exposure to rash illness during pregnancy existed. Information was not available on the sources of exposure for these women, on whether these rash illnesses or exposures to rash illness were reported to the medical staff providing their prenatal care, and on whether therapeutic abortions were considered. Also, information on the total number of therapeutic abortions done as a result of the 1979 outbreak was not available, although—as mentioned earlier—two such events were reported to the DHS.

In addition to the confirmed and probable cases presented in Figure 2, during the 1979-1980 year four cases of possible CRS (compatible clinical findings that did not quite meet the criteria for a probable case) and four cases of infection only (laboratory evidence of congenital rubella infection without apparent defects) were reported from the San Francisco Bay Area counties. These additional cases represented increases over the corresponding counts for the rest of the state and for the San Francisco Bay Area counties in the preceding three years.

Discussion

While rubella is a reportable disease in California, most cases of this usually mild illness are not reported; many are not even clinically recognized. Nonetheless, the data on reported cases shown in Figure 1 reflect the 1979 rubella outbreak in the San Francisco Bay Area. An increment in rubella cases reported from the rest of the state is noted for 1977, but this is suspected to be largely artifact, reflecting diagnoses made during a large measles outbreak that erupted in Southern California early that year.

Congenital rubella case reporting is presumably better than that for postnatal rubella, but underreporting exists, due largely to misdiagnosis (especially of cases where defects are not discovered in the neonatal period) and lack of interest in reporting.[1] Could the 1979-1980 increase in reported cases of CRS in infants born in San Francisco Bay Area counties be an arti-

fact due to changes in diagnostic and reporting thoroughness?

The 1979 outbreak and attendant publicity undoubtedly generated concern, so that it is likely that more pregnant women reported either rash illness or exposure to persons with rash illness to their obstetricians, thereby promoting increased attention to the possibility of CRS in the infants subsequently delivered. The 1979-1980 increase in reports of infants with rubella infection only (without any apparent defects) suggests that this phenomenon occurred. Most of the 13 CRS cases in the San Francisco Bay Area had major CRS stigmata, which should have promoted efforts to obtain laboratory confirmation even in the absence of maternal rash illness or exposure histories (Table 1); however, 5 of these cases might have gone undiagnosed or unreported had not the medical staff at one referral medical center made a special effort to assure that suspected cases were studied for laboratory confirmation and reported if confirmed. Staff at this medical center are certain, nevertheless, that the 1979-1980 increase in CRS cases was a real one and not simply a reflection of heightened diagnostic attentiveness.

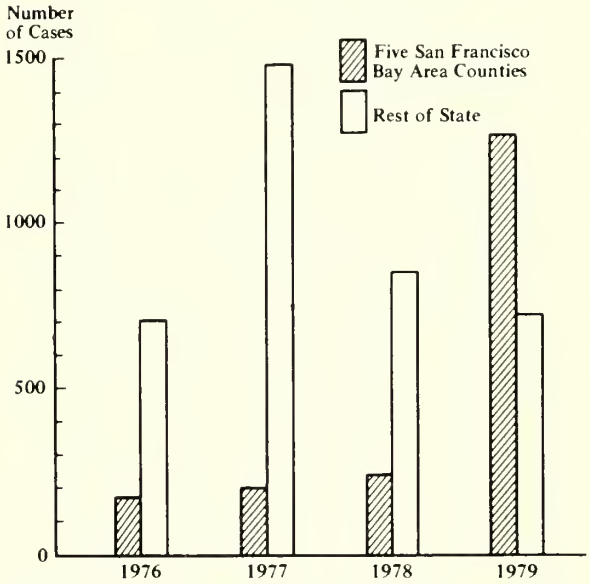

Figure 1.—Reported cases of rubella in California for the calendar years 1976 through 1979.

Poorer reporting of cases of CRS in infants born outside of the San Francisco Bay Area is suggested by Figure 2, in that for the first three years the number of reported CRS cases for the five San Francisco Bay Area counties nearly equals that for the rest of the state, even though these counties comprise only a fifth of the state's population. Three laboratories in Southern California, where over half of the state's population resides, carry

TABLE 1.—*Clinical and Laboratory Features of San Francisco Bay Area Infants With Congenital Rubella Syndrome, Born Between July 1979 and August 1980*

	Case Number												
	1	2	3	4	5	6	7	8	9	10	11	12	13*
Clinical and laboratory features													
Cataracts	..	x	x	x	x	x	x	x	..	..	..	x	..
Mental/developmental retardation	..	..	..	..	..	..	..	..	x	..	..	x	..
Hearing loss	..	x	..	..	x	x	..	..	..	..	..	..	..
Congenital heart disease													
Patent ductus	x	x	..	..	x	x	..	..	x	..	..	x	x
Pulmonic stenosis	..	..	..	..	..	..	x	x	x	..	..	..	..
Unspecified type	..	..	x	x	..	..	..	..	..	x	..	..	..
Meningoencephalitis	..	x	..	..	..	..	..	..	..	..	..	..	..
Microcephaly	..	..	..	..	..	..	..	..	..	..	..	x	x
Low platelet count and/or purpura	x	x	..	..	..	x	x	x	..	..	x	..	..
Enlarged spleen	..	x	..	..	x	..	x	x	..	..	x	..	..
Enlarged liver	..	x	..	..	x	..	x	x	x	..	x	..	..
Long bone radiolucencies	x	..	..	..	..	x	x	x	..	..	..	..	..
Congenital glaucoma	..	..	..	..	..	..	..	..	..	..	..	..	..
Jaundice (onset within 24 hours)	..	..	..	..	..	..	..	..	..	..	..	..	..
Pigmentary retinopathy	..	..	..	..	..	..	..	..	..	..	..	..	..
Laboratory confirmation													
Rubella virus isolated (from throat, N/P, urine, lens, etc.)	x	..	x	x	x	x	x	x	x	x	x	..	..
Rubella IgM antibody	..	x	..	..	..	x	..	..	..	x	..	..	..

N/P = nasopharyx

*Mother had history of rash illness in early pregnancy. Shortly after birth, serum rubella HI antibody titers for both the mother and infant were 1:512. (HI = hemagglutination inhibition)

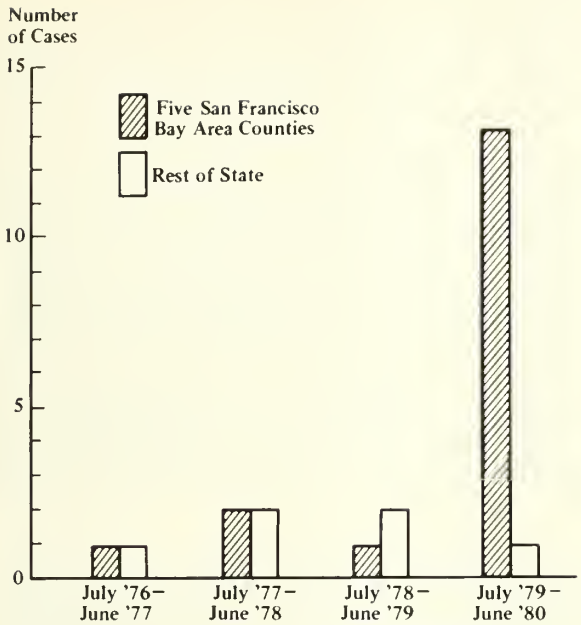

Figure 2.—Confirmed or probable cases of congenital rubella syndrome reported in California for the July-June years 1976-1977 through 1979-1980.

out rubella virus isolations. Records from these laboratories were not reviewed, and it may be that underascertainment of laboratory-confirmed cases was greater in Southern California. However, there is no reason to suspect that the degree of underascertainment changed during the time shown in Figure 2, and, thus, no evidence exists for a secular change in CRS incidence outside of the five San Francisco Bay Area counties.

Thus, while increased diagnostic and reporting thoroughness played some role, we strongly suspect that most of the observed 1979-1980 increase in San Francisco Bay Area cases of CRS is real and is a consequence of the 1979 outbreak. This episode should serve as a reminder that, despite the administration of more than 100 million doses of rubella vaccine in the United States during the past 11 years, rubella is still a relatively common disease in this country, capable of producing outbreaks followed by groups of CRS cases. As was the case in this episode, most recent rubella outbreaks have involved predominantly older teenagers and young adults—that is, the age group in which pregnancy is most common.[1] The economic impact of a CRS case is substantial. The average lifetime medical cost of such a child has been estimated to be $161,000 in 1975 dollars, a figure that does not include indirect costs that result from loss of productivity due to disability or premature death.[2]

While information on rubella immunization histories and reasons for lack of prior immunization was not obtained on the mothers of the infants with CRS associated with this outbreak, such information was secured for a similar outbreak that occurred in Chicago in 1978.[3] In the latter outbreak, investigation of mothers of 30 infants with CRS showed that none had been immunized. Two thirds of them were unmarried and, therefore, could not have been helped by premarital screening. Others were primiparas, and thus could not have been helped by previous prenatal screening and postpartum immunization. Moreover, it was found that only a small minority of seronegative women who had delivered babies in a Chicago area hospital that was surveyed had received rubella vaccine postpartum.

To prevent recurring cycles of rubella outbreaks and subsequent clusters of CRS cases, high priority must be given to the rubella immunization recommendations of the United States Public Health Service.[4]

First, essentially all girls and boys should be immunized against rubella at a young age (preferably, rubella vaccine is given in combination with measles and mumps vaccines at 15 months of age). To insure near-universal immunization and resultant "herd immunity," emphasis must be placed on rigorous enforcement of the laws, which are now in effect in virtually all 50 states, requiring rubella immunization for school entry.

Second, emphasis must also be placed on selective immunization of females of childbearing age who are known or suspected to be susceptible to rubella. These women must not be pregnant at the time the vaccine is administered and should understand that they should avoid pregnancy for three months after immunization. Suggested "checkpoints," that is, times when or where immunization can be given to women include the following: (1) when entering college or military service, (2) just before marriage, (3) immediately after childbirth and (4) while attending family planning clinics.

Clearly, however, there are problems in establishing programs to immunize postpubertal women. California has had a premarital rubella serological screening requirement since 1974, but a number of factors have hindered its effectiveness: (1) about 18 percent of live births in the state are to unmarried women, some of whom have never been married and, thus, have not been screened;

(2) "confidential" marriages and out-of-state marriages, both of which usually escape the screening requirement, now comprise almost 40 percent of marriages by Californians; (3) an unpublished survey conducted in 1976 by the DHS on a group of women identified as seronegative at premarital screening found that only a fourth of them had obtained rubella immunization two to three months after marriage, though another 60 percent stated that they intended to do so. Another survey found that many California women who had been screened serologically just before marriage were unaware of the result.[5] In Colorado and Rhode Island, premarital rubella screening requirements appear to have operated somewhat more effectively than in California, possibly because in these other programs, most of the testing is done in state laboratories and counseling of seronegative women on the need for immunization is built into the notification system.[6,7] With all programs to immunize postpubertal women there is the problem of inadvertent immunization just before or during early pregnancy; these episodes produce considerable anxiety and sometimes result in therapeutic abortions, though the teratogenicity risk associated with the vaccine is very small and possibly nil.[3]

Conclusion

In spite of the difficulties cited, we feel that the threat of rubella infection in early pregnancy remains sufficiently great that programs to identify and immunize females of childbearing age should be strengthened and pursued aggressively. Women discovered to be seronegative for rubella must be given concise, effective counseling on the nature of the threat of CRS and the need for rubella immunization at an appropriate time. These activities are particularly important at present, because several years must elapse before the herd immunity, resulting from implementation of recently enacted requirements for school-entry rubella immunization, can be expected to exert its full impact.

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Computerized Tomographic Diagnosis of Paracardiac Masses

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Paracardiac masses may alter the cardiac contour seen on roentgenograms of the chest so as to mimic configurations associated with cardiac disease. Recently, the use of computerized transmission tomography has proved valuable as a noninvasive method of distinguishing between intrinsic cardiac disease and paracardiac masses. In some cases, the procedure obviates the need for preoperative cardiac catheterization.

PARACARDIAC MASSES may cause abnormalities of the cardiac contour that mimic configurations associated with cardiac disease. In the past it has been necessary to rely on careful auscultation, electrocardiography, fluoroscopy and cardiac catheterization to distinguish intrinsic cardiac disease from paracardiac masses. In recent years noninvasive techniques such as computerized transmission tomography (CTT) and two-dimensional real-time echocardiography have favorably complemented the older methods.

This report describes the cases of seven patients seen during the past five years in whom chest roentgenograms were interpreted as indicative of intrinsic cardiac disease but in whom noninvasive studies showed paracardiac masses. In six of these patients cardiac catheterization was eventually done. In the seventh and most recent patient treated, extracardiac disease was demonstrated by CTT, obviating the need for preoperative catheterization.

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Reports of Cases

CASE 1. An 18-year-old asymptomatic man was referred for evaluation of abnormal findings on a roentgenogram of the chest, which suggested absence of the left pericardium and pericardial cyst (Figure 1). Results of a physical examination were normal except for a palpable impulse felt in the left second intercostal space. An electrocardiogram showed no abnormalities.

Catheterization of the right side of the heart showed pressures and oxygen saturation to be normal. An angiogram of the left atrium gave normal findings, with no evidence of partial absence of the left pericardium. However, angiography showed compression of the right atrium.

A CTT scan demonstrated a large cystic mass extending from the right to the left cardiac border (Figure 2). At operation a lobulated cystic mass was found that originated from the thymus gland and extended anteriorly across the heart. It was

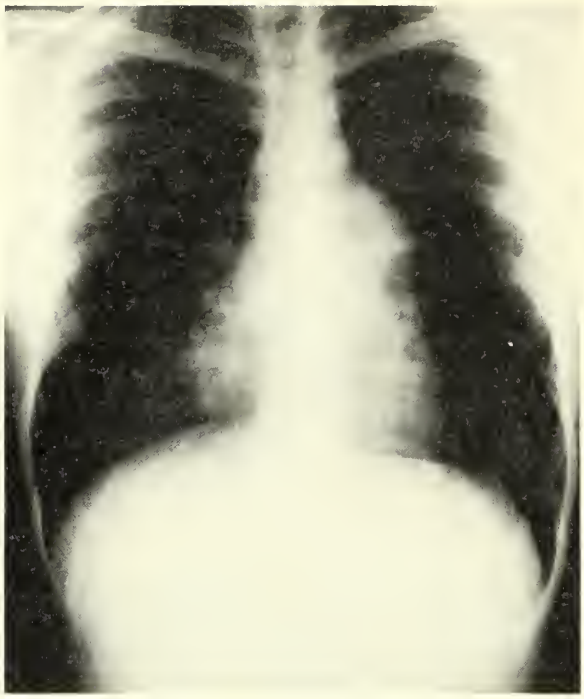

Figure 1.—Posteroanterior roentgenogram of the chest showing prominent bulging of the left and right borders of the heart. The bulging was caused by a thymic cyst with Hodgkin's disease, originating in the anterior mediastinum.

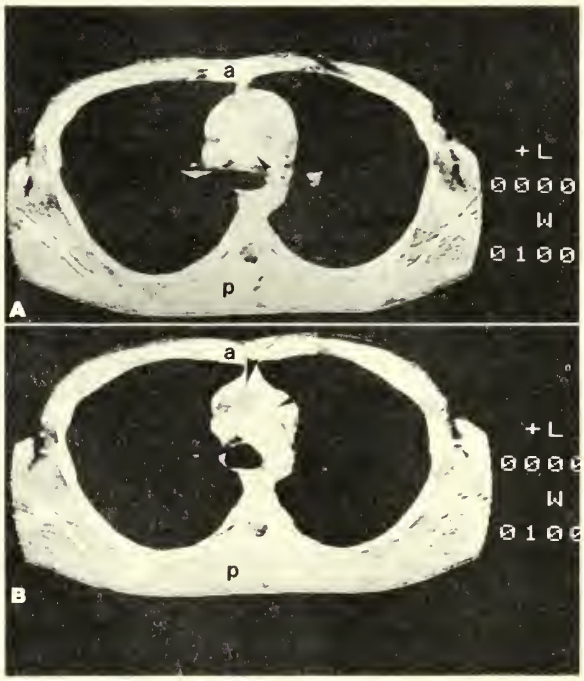

Figure 2.—Contrast-enhanced CTT scans at the level of the carina **(A)** and near the bifurcation of the main pulmonary artery **(B)**. Arrowhead in **(A)** identifies the aorta, which is surrounded by tumor anteriorly. In **(B)**, small arrowhead identifies the pulmonary artery. The cystic component of the mass is shown (large arrowhead) (a = anterior; p = posterior).

excised in toto. Pathological examination of the excised tissue showed nodular sclerosing Hodgkin's disease, originating in a thymic cyst.

Case 2. A 57-year-old man presented with exertional dyspnea and a heart murmur. Previously, he had been found to have obstructive

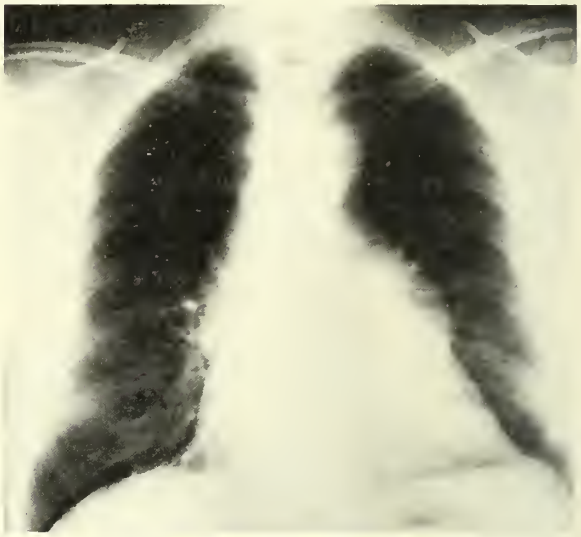

Figure 3.—Posteroanterior roentgenogram of the chest shows a right-sided aortic arch and a tortuous descending aorta located to the right of the spine. There is a large mass projecting from the upper portion of the left cardiac border. Pulmonary vessels are visible through this mass, which proved to be a pericardial pseudocyst.

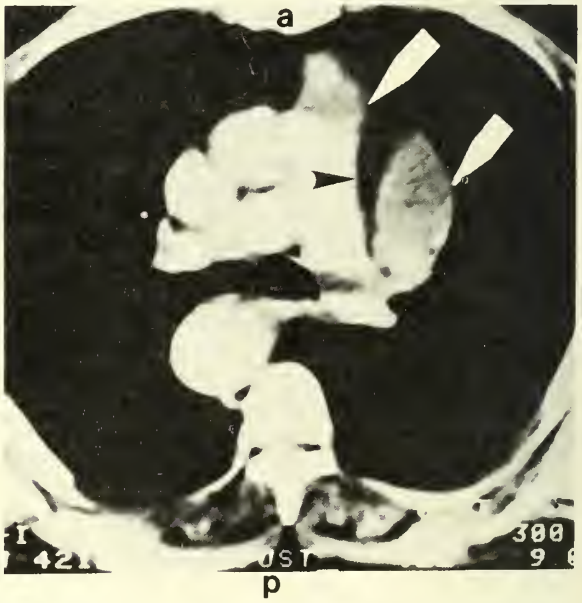

Figure 4.—CTT scan at the level of bifurcation of the pulmonary artery. Bilobed cystic mass (pericardial pseudocyst) is located anterior and to the left of the main pulmonary artery (large arrows). Note the fat plane (arrowhead) separating the cyst from the pulmonary artery and right ventricle (a = anterior; p = posterior).

hypertrophic cardiomyopathy at cardiac catheterization, and ventricular septal myomectomy was carried out in 1965. In 1979 a roentgenogram of the chest showed a localized mass extending from the upper left cardiac border (Figure 3). A right aortic arch was present. An S_1 gallop with a grade 2/6 murmur at the left sternal border, radiating to the apex, was noted. Electrocardiographic findings included left atrial enlargement and left bundle branch block. Asymmetric septal hypertrophy without systolic anterior motion of the mitral valve was seen at M-mode echocardiography. Angiography showed no evidence of ventricular false aneurysm or herniation of the atrial appendage, though a defect in the left pericardium was found. A computerized transmission tomographic scan showed an oval mass located in the left anterior mediastinum adjacent to the pulmonary artery and extending down the left ventricular border (Figure 4).

Figure 5.—Posteroanterior roentgenogram of the chest showing a mass in the region of the main pulmonary artery. The mass gives the appearance of poststenotic dilatation of the pulmonary artery (From Vieweg WVR, Brodhead CL, Neil DJ, et al: Hodgkin's disease of the anterior mediastinum presenting as pulmonic stenosis. South Med J 69:1094-1096, Aug 1976).

At thoracotomy a pericardial pseudocyst located in the left retrocardiac area was found; it extended along the left upper margin of the heart. This mass was not present at the time of initial operation in 1965.

Case 3. A 27-year-old woman was seen because of tightness in her chest and shortness of breath. She had no previous history of cardiac disease. Abnormal findings on a roentgenogram of the chest were interpreted as enlargement of the main pulmonary artery (Figure 5).

On physical examination a grade 3/6 harsh systolic ejection murmur over the pulmonic area was noted, which did not vary with respiration. An electrocardiogram showed right ventricular hypertrophy. A right ventriculogram showed compression and displacement of the great vessels by an anterior mediastinal mass; however, the pulmonary artery was not enlarged.

At operation there was a grapefruit-sized mass embracing and compressing the great vessels. Histological examination indicated nodular sclerosing Hodgkin's disease.

Cases 4 through 7. In four additional patients, roentgenograms of the chest showed mediastinal

Figure 6.—Posteroanterior roentgenogram of the chest showing a mass in the region of the main pulmonary artery. The mass gives the appearance of enlargement of the main pulmonary artery; however, it proved to be a Hodgkin's lymphoma.

TABLE 1.—*Diagnostic Information on Seven Patients With Paracardiac Masses*

Patient	*Age/Sex*	*Radiographic Working Diagnosis*	*Postcatheterization/ Noninvasive Diagnosis*	*Surgical Findings*
1	18/M	Pericardial cyst; partial absence of left pericardium	Mediastinal mass	Thymic cyst with Hodgkin's lymphoma
2	57/M	False cardiac aneurysm	Pericardial cyst	Pericardial pseudocyst
3	27/F	Pulmonic stenosis	Mediastinal mass	Hodgkin's disease
4	22/M	Idiopathic enlargement of the right atrium	Mediastinal mass	Mediastinal teratoma
5	21/M	Congenital partial absence of the left pericardium	Mediastinal mass	Thymoma
6	28/M	Pericardial fat pad	Pericardial mass	Desmoid tumor
7	30/F	Enlargement of the main pulmonary artery	Mediastinal mass	Hodgkin's disease

masses that masqueraded as intrinsic cardiac disease.[1-3] These included, respectively, mediastinal teratoma masquerading as idiopathic enlargement of the right atrium, thymoma masquerading as congenital partial absence of the left pericardium, desmoid tumor presenting as a pericardial fat pad, and Hodgkin's disease in a thymus presenting as enlargement of the main pulmonary artery (Figure 6). In the last patient a CTT scan convincingly showed a solid anterior mediastinal mass, which obviated the need for preoperative cardiac catheterization and angiography.

Discussion

The current series of cases (Table 1) emphasizes that paracardiac masses may alter the cardiac contour in such a manner as to mimic the configurations of intrinsic cardiac disease. Findings of a physicial examination and electrocardiogram may show abnormalities that support the diagnosis of a primary cardiac lesion—particularly when extracardiac masses cause compression of the pulmonary artery.[4-7] Such paracardiac masses that mimic heart disease are usually mediastinal solid or cystic neoplasms or pericardial cysts and diverticulae. The mediastinal neoplasms that cause such apparent changes in cardiac contour usually originate in the radiographic anterior mediastinum as defined by Felson.[8] The solid and cystic masses arising in this area are legion and include thymoma, thymic cyst, teratoma, germinal cell tumors, pericardial cysts and diverticula, foramen of Morgagni hernia, lymphoma, lipoma, fibroma, parathyroid adenoma and paraganglionoma.

Often the extracardiac location of such lesions can be determined by fluoroscopy, oblique and overpenetrated chest roentgenograms, and linear tomography. A valuable addition to these techniques is CTT with contrast media, which can usually determine whether the lesion involves an extracardiac process and whether it has extended to the heart or pericardium.[9-11] Cardiac catheterization and angiography can exclude intrinsic cardiac abnormalities, but they provide less information regarding the nature, location and extent of the responsible extracardiac process than does CTT.[9-11] Fatty tumors that infiltrate the mediastinum have been confused with primary cardiac disease[12]; however, CTT has been reliable in detecting the fatty nature of the mediastinal process.[9,13]

Pericardial cysts infrequently mimic primary cardiac disease; however, most of these cysts can be recognized by their characteristic location at cardiophrenic angles and by the fact that the mass is usually round and abuts the hemidiaphragm and anterior chest wall.[14]

A particularly difficult problem with the cases under discussion was that the paracardiac masses caused abnormalities in the cardiac contour that suggested cardiac entities usually recognized by a specific configuration on roentgenograms of the chest. For example, idiopathic dilatation of the right atrium is considered when a prominent right atrial shadow is observed in the absence of other cardiac findings.[15] Enlargement of the main pulmonary artery segment in the presence of a systolic murmur suggests a diagnosis of either valvular pulmonic stenosis or idiopathic dilatation of the pulmonary artery. Because masses extrinsic to, but constricting, the pulmonary artery may cause a systolic murmur, confusion regarding the nature of the roentgenographic abnormality may be compounded.

A mass in the anterior mediastinum superimposed on the main pulmonary artery segment may be suggested by observing the hilum overlay, the hilar convergence signs, or both.[8] Further, a pseudoaneurysm of the left ventricle usually has

a characteristic radiographic appearance, and rapid enlargement in size of the contour abnormality is particularly suggestive of this entity. Pseudoaneurysm has been observed as a complication of cardiotomy.

Conclusion

These cases emphasize that paracardiac masses should be considered in the differential diagnosis of contour abnormalities of the cardiac shadow, even when the cardiac configuration seems characteristic of a specific cardiac diagnosis. Computerized transmission tomography has been particularly useful in delineating the extracardiac nature of these types of lesions.

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Refer to: Strauchen JA: Malignant lymphomas: Cell surface markers and advances in classification (Medical Progress). West J Med 135:276-284, Oct 1981

Malignant Lymphomas: Cell Surface Markers and Advances in Classification

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Identification of cell surface markers permits detailed analysis and classification of the cells involved in the immune response. Application of these techniques to the study of malignant lymphomas has led to our understanding of these tumors as neoplasms of specific elements of the immune system. This approach, which emphasizes functional characteristics of the neoplastic cells, promises to revolutionize the diagnosis and classification of the lymphomas and replace classifications based solely on morphology.

THE PAST DECADE has witnessed a rapid growth of interest and research in malignant lymphomas. This has been stimulated both by the recognition of the therapeutic responsiveness of some of these tumors and by the explosive growth of information in immunology and the emergence of cellular immunology as a discipline. The development of cell surface markers has permitted the recognition and identification of specific physiological classes of lymphoid cells involved in the immune response. Application of these techniques to the study of the malignant lymphomas has led to our current understanding of these tumors as neoplastic proliferations of specific elements of the immune system. This approach now promises a rational classification of the lymphomas, which will supplant confusing and misleading classifications based solely on morphology. This review will consider the markers currently in use, our present understanding of the ontogeny of the immune system and the classification of specific lymphomas as neoplasms of elements of the immune system. The current histopathologic classifications will also be considered.

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Markers and Ontogeny of the Immune System

The major physiological classes of lymphoid cells are distinguished by a variety of cell surface markers.[1] These appear on lymphoid cells in a characteristic sequence accompanying cellular differentiation and relate to immune cell function. Identification of markers on a cell (cell "phenotyping"), therefore, may indicate the physiological class of the cell (for example, B, T or true histiocytic) as well as its stage of development (Figure 1). As applied to lymphomas, this type of information permits classification of the lymphoma as to cell of origin as well as information as to the level at which neoplastic differentiation has been "blocked."[2] The marker sequences for the major cell classes are distinct and will be discussed separately.

B Cells

Circulating mature B cells carry a variety of readily detectable markers: surface immunoglob-

ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
C′ = complement
CIg = cytoplasmic immunoglobulin
CLL = chronic lymphocytic leukemia
SIg = surface immunoglobulin
TdT = terminal deoxynucleotidyl transferase
WDLL = well-differentiated lymphocytic lymphoma

ulin (SIg), Ia-like antigens, and receptors for complement and for the Fc portion of IgG.[3,4] Surface immunoglobulin is most readily detectable by immunofluorescence with heterologous antisera to the major classes of human immunoglobulins: IgA, G, D, M and the light chains *k* and λ. Nonspecific binding of antibody to Fc receptors may be circumvented by using Fab fragments rather than whole antibody. Receptors for complement (C′) are detected by a rosette reaction using sheep erythrocytes sensitized with antibody (IgM) and complement, so-called EAC rosettes. The sensitized antibody-complement coated erythrocytes will bind specifically to lymphocytes expressing receptors for complement. Fc receptors are detected by a similar rosetting reaction using erythrocytes sensitized only with antibody (IgG), so-called EA rosettes. The antibody coated erythrocytes bind specifically to lymphocytes expressing receptors for the Fc portion of IgG.

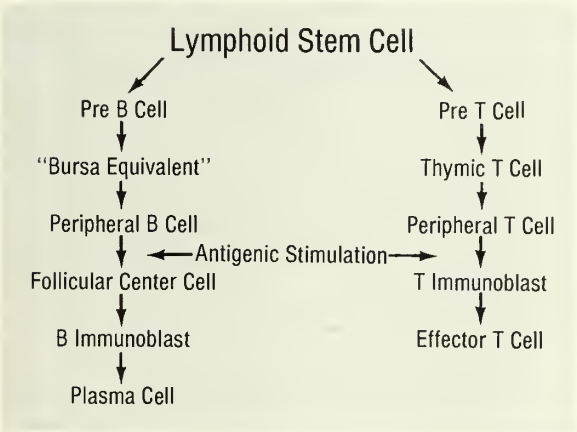

Figure 1.—Ontogeny of the cellular immune system.

TABLE 1.—*Markers of Developing Lymphoid Cells*

	CIg	*SIg*	*C′*	*TdT*	*E rosette*
Stem cell	−	−	−	?	−
Pre-T cell	−	−	−	+	−
Thymic T cell	−	−	−	+	+
Peripheral T cell	−	−	−	−	+
T immunoblast	−	−	−	−	+
Pre-B cell	+	−	−	+	−
Peripheral B cell	−	+	+	−	−
B immunoblast	+	+	+	−	−
Plasma cell	+	−	−	−	−

C′ = receptor for complement; CIg = cytoplasmic immunoglobulin; E rosette = receptor for sheep erythrocytes; SIg = surface immunoglobulin; TdT = terminal deoxynucleotidyl transferase

The earliest identifiable B cell precursor in the bone marrow is the pre-B cell (Table 1). These morphologically lymphoblast-like cells lack the specific B cell markers noted above but demonstrate a small amount of intracytoplasmic IgM (CIg).[5] With further maturation, CIg disappears as SIg makes its appearance. Receptors for the components of complement also appear in sequence during B cell maturation.[6] With antigenic stimulation, B cells undergo a proliferative response. The region of B cell proliferation in the lymph node is the follicular center or germinal center. In these regions, Lukes and Collins[7] have described a characteristic morphological transformation of the small lymphocyte through stages of small and large cleaved cell, small and large noncleaved cell and B immunoblast. The cleaved morphology consisting of a clefted or indented nucleus is thought to be characteristic of follicular center B lymphocytes. The follicular B lymphocyte also demonstrates increased SIg and C′ receptors. The immunoblast or fully transformed B cell is considered to be the immediate precursor of the plasma cell, the antibody-secreting effector cell of the B cell lineage. At the immunoblastic stage of transformation, cytoplasmic immunoglobulin again makes its appearance. With terminal plasma cell differentiation, the B cell surface markers (SIg, Ia, C′ and Fc) are lost and cytoplasmic immunoglobulin predominates.

T Cells

The major surface marker of the mature T cell is a receptor for sheep erythrocytes, the so-called E rosette reaction. The nature of the receptor and its binding site on the sheep erythrocyte is not understood. T cells are also recognized by reactions with specific alloantisera or monoclonal antibodies.[8] Certain T cell classes also possess receptors for IgG and IgM Fc portions. The earliest recognizable T cell precursor in the marrow is the pre-T cell (Table 1). This cell lacks receptors for sheep erythrocytes but reacts with certain anti-T antisera. The pre-T cell also contains a peculiar DNA synthetic enzyme, terminal deoxy-

nucleotidyl transferase (TdT).[9,10] This enzyme has the characteristic property of adding bases nonspecifically to a DNA terminus. It is, therefore, unlike the usual DNA polymerases, which are template dependent.

It has been postulated that TdT may function as a somatic mutagen and play a role in the generation of immunologic diversity.[11] Although originally thought to be a marker for T cell precursors, TdT has since been recognized in pre-B cells as well and may be a marker for certain classes of lymphoid stem cell.[5,12] Normal TdT activity in the marrow is thought to be due to the presence of these cells. Pre-T cells from the marrow migrate to the thymus where they differentiate under the influence of the thymic epithelium. Thymic T cells possess both receptors for sheep erythrocytes and TdT, which accounts for the high level of TdT found in this organ.[12] Mature circulating T cells retain receptors for sheep erythrocytes, but TdT activity is lost. Curiously, although immunoblast transformation occurs with antigenic or mitogen stimulation, TdT activity is not regained. The T immunoblast or transformed T cell is the precursor of T effector cells, which mediate delayed hypersensitivity. The atypical or reactive lymphocytes, which circulate in viral or hypersensitivity illnesses, are closely related to immunoblasts of T and B origin.[13] Certain classes of T cells exhibit a characteristic morphology described as convoluted or cerebriform.[7] These terms refer to elaborate nuclear infoldings resembling the cerebral gyri and sulci. This morphology is associated with some neoplastic T lymphoblasts[14] and with T lymphocytes in the skin, particularly those associated with mycosis fungoides and Sézary syndrome.[15]

Macrophages or "True" Histiocytes

Much confusion has arisen from the uncritical use of the term "histiocyte" in morphological pathology for any large lymphoreticular cell. Properly speaking, the macrophage or true histiocyte is a phagocytic cell derived from circulating blood monocytes and, ultimately, from the bone marrow.[16] The marrow origin of monocytes and tissue histiocytes has been established by both marrow culture and marrow transplantation experiments.

Histiocytes (and their precursors, monocytes) possess Ia-like antigens and receptors for complement and Fc.[17] They lack endogenous surface immunoglobulin (but may acquire exogenous immunoglobulin by virtue of avid Fc receptors). Histiocytes are rich in acid hydrolases, particularly lysozyme or muramidase.[18] Immunoperoxidase staining for muramidase has been used as a specific marker. Phagocytosis of latex particles or sensitized erythrocytes has also been used as a histiocytic marker.

Homing and Lymphocyte Domains

Early marker experiments showed that the distribution of lymphocyte types within a lymph node is not random, but that specific domains exist. B cells are distributed predominantly in the cortical follicles and medullary cords of lymph nodes and in the follicles or white pulp of the spleen. T cells are predominantly distributed in the paracortical or interfollicular region of lymph nodes and in the periarteriolar sheaths of the spleen. Histiocytes are distributed in the marginal and medullary sinuses of the lymph node and in the red pulp sinuses of the spleen. These data are confirmed by "experiments of nature"—that is, the immunodeficiency disorders: B cell immunodeficiency (Bruton-type agammaglobulinemia) results in primarily follicular depletion whereas T cell immunodeficiency (DiGeorge's syndrome) results in primarily paracortical depletion. Although the mechanisms of lymphocyte homing are not well understood, they presumably involve recognition of cell surface signals.[19] These are partially preserved in the malignant lymphomas as many lymphomas of B, T or histiocytic origin tend to involve preferentially the corresponding lymph node domain.[20]

Malignant Lymphomas

Given the presently available detailed information about the normal ontogeny of the immune system, it is possible to consider the malignant lymphomas as neoplastic proliferations of specific elements of the immune system whose differentiation has been "blocked" at certain levels of development (Table 2). This approach to classification will likely supplant those based purely on morphological description. However, because of the vast volume of clinicopathologic correlation related to the morphological classifications, these approaches are still clinically useful and necessary. The original classification of the malignant lymphomas evolved during the first half of this century and recognized three categories of lymphosarcoma, reticulum cell sarcoma and giant follicular lymphoma. In modern terms, these

roughly correspond to lymphocytic or small cell lymphoma, histiocytic or large cell lymphoma and nodular lymphoma. This classification has subsequently been expanded in the two modern American classifications: that of Rappaport[21] and that of Lukes-Collins.[22a] The Rappaport classification (Table 3) was proposed as a purely descriptive approach and has served well clinically, although we now know several of the terms and concepts are biologically incorrect. The Lukes-Collins classification (Table 4) is newer and proposes a functional or immunologic classification.[22b,22c] Recently, a National Cancer Institute-sponsored study has led to a new working formulation of the non-Hodgkin's lymphomas (Table 5).[23] The formulation is based on prognostic divisions among the lymphomas and uses a nomenclature which although descriptive is biologically correct. It is hoped that the formulation, which facilitates a translation of terminology among the major classifications, will permit a greater degree of comparability among clinical studies. In discussing some of the specific malignant lymphomas, I will attempt to give the classification in each of the two major American systems and the proposed formulation.

TABLE 2.—*Lymphomas as Neoplasms of Specific Cell Classes of the Immune System*

B Cell	
Pre-B cell	ALL (rare)
Medullary B cell	CLL Small lymphocytic lymphoma
Follicular B cell	Follicular lymphomas Large cell lymphoma Burkitt's lymphoma
B Immunoblast	Large cell lymphoma
T Cell	
Pre-T cell	ALL (common)
Thymic T cell	ALL (uncommon) Lymphoblastic lymphoma
T cell	CLL (rare) Sézary—mycosis fungoides
T immunoblast	Large cell lymphoma (rare)
Histiocytic	
Histiocyte	Malignant histiocytosis Hodgkin's disease (?)

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia.

TABLE 3.—*Non-Hodgkin's Lymphoma: Rappaport Classification (1966)**

Nodular or diffuse
- Undifferentiated
- Lymphocytic lymphoma, well-differentiated
- Lymphocytic lymphoma, poorly differentiated
- Mixed lymphocytic—histiocytic
- Histiocytic lymphoma

*From Rappaport.[21]

TABLE 4.—*Non-Hodgkin's Lymphoma: Lukes-Collins Classification**

U cell (undefined)	
T cell	B cell
Small lymphocyte	Small lymphocyte
Convoluted lymphocyte	Plasmacytoid lymphocyte
Cerebriform cell of Sézary's syndrome and mycosis fungoides	Follicular center cell types (Follicular, follicular and diffuse, diffuse) Small cleaved Large cleaved Small noncleaved Large noncleaved
Lymphoepithelioid cell	
Immunoblastic sarcoma	Immunoblastic sarcoma
Histiocytic	

*From Lukes.[22c]

TABLE 5.—*Non-Hodgkin's Lymphoma: A Working Formulation for Clinical Usage**

Low grade
- Small lymphocytic
- Follicular, small cleaved cell
- Follicular, mixed small cleaved and large cell

Intermediate grade
- Follicular, large cell
- Diffuse, small cleaved cell
- Diffuse, mixed small cleaved and large cell
- Diffuse, large cell—cleaved and noncleaved

High grade
- Diffuse, large cell—immunoblastic
- Small noncleaved cell (Burkitt and non-Burkitt)
- Lymphoblastic (convoluted and nonconvoluted)

*From Berard.[23]

Malignant Lymphomas of B Cell Origin

Small Lymphocytic Lymphomas

[*Well-differentiated lymphocytic lymphoma (Rappaport). Small lymphocytic lymphoma (Lukes-Collins). Low-grade lymphoma, small lymphocytic (Working Formulation).*]

These are lymphomas composed of small round lymphocytes morphologically resembling the small peripheral blood lymphocyte. The morphology is indistinguishable from that of chronic lymphocytic leukemia (CLL) of which it appears to represent the tissue phase. Waldenström's macroglobulinemia and the heavy chain diseases are closely related lymphomas demonstrating plasmacytoid features.[24]

Well-differentiated lymphocytic lymphoma (WDLL) and CLL are almost always B cell neoplasms.[25] Rare instances of T cell CLL have been described and represent a distinct clinical entity, with a high incidence of skin and central nervous

system involvement.[26] In these cases the cells are mature T cells with positive E rosettes and absent TdT.

The much more common B cell cases demonstrate surface immunoglobulin (IgM or IgM + IgD) and receptors for complement.[27] The SIg is restricted to a single light chain class, *k* or λ, indicating the monoclonal nature of the proliferation. This feature may be diagnostically useful occasionally in distinguishing a reactive lymphocytic proliferation which does not show light chain restriction. Recent data have suggested a similar restriction of complement receptor expression, the majority of cases showing only receptors for C 3 d.[6] The marker pattern of cells from WDLL is identical to that of CLL, which indicates the fundamental relatedness of the two conditions.[27] B cells from either CLL or WDLL demonstrate a low-density pattern of SIg staining and a weak receptor for complement. Studies of normal lymph nodes demonstrate that these are the features of medullary B lymphocytes, suggesting that both CLL and WDLL arise from the small medullary lymphocyte.[2] This is consistent with the histological observation that WDLL is always a diffuse process unrelated to follicular centers. Occasionally CLL or WDLL may terminate in a rapidly progressive large cell lymphoma (so-called Richter's syndrome). In the cases examined, the surface markers and light chain restriction are retained, which suggests this phenomenon is a result of clonal evolution.[28] Lymphocytic lymphoma of so-called intermediate differentiation is a closely related entity that appears to arise from the small lymphocytes of the perifollicular cuff.[29]

Nodular Lymphomas

[*Nodular poorly differentiated lymphocytic, nodular mixed, nodular histiocytic (Rappaport). Follicular center cell lymphoma, small cleaved, large cleaved, large noncleaved (Lukes-Collins). Low-grade lymphoma, follicular, small cleaved cell, mixed small cleaved and large cell; intermediate-grade lymphoma, follicular, large cell (Working Formulation).*]

The relatively good prognosis of lymphomas with a nodular pattern was recognized early in this century, with a serious debate as to whether "giant follicular lymphoblastoma" was actually a malignant disease. Although Rappaport introduced the term nodular lymphoma as a purely descriptive term, it is now appreciated that these tumors arise from and attempt to recapitulate the cells of the lymph node follicle.[3] The term follicular lymphoma is therefore more apt. The bewildering array of cytologic features observed in these tumors is now appreciated to reflect the cytologic pleomorphism of the follicular center.

Marker studies of nodular lymphomas demonstrate them invariably to be composed of monoclonal B cells.[3,30] The cells possess a high-density pattern of SIg (IgM or IgM + D) and a strong complement receptor. These are the features of the normal follicular center cell, which supports the concept of nodular lymphomas as neoplasms of follicular lymphocytes.[3]

Cystologically, the hallmark of follicular lymphocytes is the cleaved cell.[7] The cleaved cell is a small or large lymphoid cell that has a deep nuclear cleft resulting in an irregular or peanut configuration. These are the cells identified by hematologists in so-called lymphosarcoma cell leukemia as "buttock" cells. Rappaport originally considered these cells poorly differentiated lymphocytes—hence, the term poorly differentiated lymphocytic lymphoma. We now appreciate that these cells are in reality well-differentiated follicular center cells.[31] The cytologic diversity of follicular lymphomas corresponds to the cytologic pleomorphism of the follicular center. The morphogenesis of follicular center cells has been elaborately described by Lukes and Collins.[7] Follicular lymphomas are classified according to the dominant cell type: small cleaved, mixed small cleaved and large cell, or large cell (Working Formulation). The biological aggressiveness appears to relate directly to the component of mitotically active large cells. Occasionally, lymphomas are observed with a diffuse pattern but composed of follicular-type cleaved cells, so-called diffuse poorly differentiated lymphocytic lymphoma (Rappaport) or intermediate-grade lymphoma, diffuse small cleaved cell (Working Formulation). These appear to represent follicular cell lymphomas that have lost the ability to form recognizable follicles and have a correspondingly worse prognosis.

Burkitt's Lymphoma

[*Undifferentiated lymphoma, Burkitt's type (Rappaport). Follicular center cell lymphoma, small noncleaved (Lukes-Collins). High-grade lymphoma, small noncleaved cell (Working Formulation).*]

Burkitt's lymphoma is a neoplasm originally identified in African children by Sir Dennis Burkitt.[32] Subsequently, cases with identical histology

have been identified in the United States.[33] Cases of Burkitt's lymphoma in the United States appear to differ from the African form of the disease in that the association with Epstein-Barr virus is much less strong, and the classic jaw tumors are seldom seen. The poorer therapeutic response of the American cases of the disease has been attributed to the higher incidence of advanced abdominal presentations.[34]

Histologically, Burkitt's lymphoma is characterized by a diffuse proliferation of mitotically very active "undifferentiated" lymphoid cells interspersed with benign phagocytic histiocytes that produce the so-called starry sky appearance. The results of immunologic marker studies suggest that the cells are not undifferentiated or stem cells as originally suggested, but are rapidly proliferating B cells.[35] In this series[35] of American cases, all eight demonstrated high-density staining for surface immunoglobulin (IgM) and a variable number of cells with receptors for complement. Lukes and Collins have suggested that the Burkitt cell is morphologically similar to a cell of the follicular center—the small noncleaved follicular center cell.[7] This suggestion is supported by the observation that early Burkitt's lymphoma may show a partially follicular pattern, with selective involvement of follicular centers.[2] Thus, Burkitt's lymphoma may be the childhood equivalent of the much more common follicular center cell lymphomas of adults.

Large Cell Lymphomas

[*Large cell or histiocytic lymphoma (Rappaport). Follicular center cell lymphoma, large cleaved and large noncleaved; immunoblastic sarcoma of B cells (Lukes-Collins). Intermediate grade lymphoma, large cell, cleaved or noncleaved; high-grade lymphoma, immunoblastic (Working Formulation).*]

The large cell lymphomas are immunologically heterogeneous, but in most series the majority (50 percent to 60 percent) appear to arise from B cells.[2] The term histiocytic lymphoma, synonymous with large cell lymphoma, is a misnomer stemming from the uncritical use of the term histiocyte for any large lymphoreticular cell. The overwhelming majority of large cell lymphomas arise from transformed lymphoid cells, with only rare examples possessing true histiocytic markers. In a series of 19 cases studied at the National Cancer Institute, 11 had B cell markers (SIg 10 C′ 9), 2 had T cell markers (E rosettes), 1 had true histiocytic markers (C′, esterase and phagocytosis) and 5 had no detectable markers (null cells).[2] Thus, the large cell histology appears to be a final common pathway for highly malignant tumors of all arms of the immune system, but most commonly B cell.

Morphological subclassification of large cell lymphomas is controversial, but it appears that subgroups can be recognized histologically. Lukes[7] divided the large cell lymphomas into follicular center types, which showed evidence of follicular center cell differentiation (large cleaved and large noncleaved) and immunoblastic types, which showed large transformed lymphoid cells with intensely pyroninophilic cytoplasm and plasmacytoid features. In a review of cases at the National Cancer Institute, the prognosis for large cell lymphomas with follicular center differentiation (large cleaved, large noncleaved and mixed follicular center cell) was superior to lymphomas without follicular center differentiation (so-called pleomorphic pyroninophilic and blastic).[36] Thus, the large cell lymphomas can be divided into at least two prognostically significant groups, the follicular center cell type and the immunoblastic type. This division has been incorporated into the working formulation.

Large cell lymphomas of non-B cell origin are difficult to recognize morphologically. Large cell lymphomas of true histiocytic origin are closely related to malignant histiocytosis *(vide infra)* of which they probably represent a tumoral phase. Occasional large cell lymphomas of T cell origin can be recognized by the presence of large cells with convoluted nuclei.[37] A recent study suggests that the presence of B or T markers may be of prognostic significance.[38]

Malignant Lymphomas of T Cell Origin

Lymphoblastic Lymphoma

[*Lymphoblastic lymphoma (Rappaport). Convoluted lymphocytic lymphoma (Lukes-Collins). High-grade lymphoma, lymphoblastic (Working Formulation).*]

Lymphoblastic lymphoma is closely related to the more familiar acute lymphoblastic leukemia (ALL).[14] Recent immunologic data suggest that ALL arises from classes of lymphoid stem cells (pre-B, pre-T, and thymic T) and that lymphoblastic lymphoma represents the tissue phase of T cell ALL.[39,40] Lymphoblastic lymphoma affects primarily adolescent boys with a high incidence thymic mass and leukemic transformation. The

histology of lymphoblastic lymphoma is identical to that of ALL in lymph nodes. The occurrence of so-called convoluted cells in this disorder has received much attention.[14] This refers to complex nuclear foldings seen in a variable proportion of both lymphoblastic lymphoma and ALL. The presence of convoluted cells is of diagnostic value but not of any special prognostic significance.[14]

Results of cell marker studies in lymphoblastic lymphoma demonstrate the features of immature thymic-type T cells.[41] More than half the cases form E rosettes, and TdT is almost invariably present.[42] This is identical to the findings in T cell ALL but is in contrast to the more common null cell ALL which is TdT-positive but does not form E rosettes. The hypothesis that lymphoblastic lymphoma is of T cell origin is supported by the selective involvement of T cell domains, including the thymus and paracortical regions of lymph nodes.

Sézary Syndrome—Mycosis Fungoides

Mycosis fungoides is a progressive skin disorder, now recognized to be a malignant lymphoma with selective skin involvement. The Sézary syndrome is a closely related condition with circulating abnormal cells, and may be considered the leukemic phase of mycosis fungoides. Although the older literature is replete with reports of Hodgkin's disease and other lymphomas developing in patients with mycosis, it is now apparent that these represent terminal visceral spread of mycosis fungoides.[43]

The Sézary-mycosis cell has a unique morphology described as cerebriform.[15] The nucleus is infolded with extreme complexity, best appreciated in plastic-embedded thin sections. This morphology may be characteristic of the skin lymphocyte, as similar cells may be seen in benign inflammatory conditions of the skin.[44] Marker studies have shown that the Sézary-mycosis cell is a mature T cell (E rosette-positive, TdT-negative), and in some cases the cells have in vitro helper T cell function.[45,46] The cells are peculiarly epidermotrophic with a propensity for infiltrating the epidermis as single cells or groups (so-called Pautrier microabscesses).[47] The special clinicopathologic features of mycosis fungoides are a direct result of this epidermotrophism. Mycosis fungoides characteristically progresses from an inflammatory premycotic phase, through a plaque phase to a tumor phase. In the early stages of the disease, regional lymph nodes show the changes of dermatopathic lymphadenitis, consisting of histiocytic hyperplasia and melanin deposition. With advanced disease, paracortical (T zone) infiltration with mycosis cells occurs and, ultimately, visceral involvement as well.[43] While still confined to the skin, treatment with electron beam may result in prolonged remission. The diagnosis of mycosis fungoides may be very difficult to confirm in the early premycotic stage as the histological findings are nonspecific. Parapsoriasis en plaque and follicular mucinosis may precede the development of mycosis fungoides. When characteristic Pautrier microabscesses (group infiltration of the epidermis by Sézary-mycosis cells) are identified, the diagnosis becomes more certain. Lymphomatoid papulosis, a benign self-limited condition may closely mimic the histological findings in mycosis fungoides.[48] The diagnosis of Sézary syndrome is based on the identification of circulating abnormal lymphoid cells, usually found in a patient with diffuse erythroderma. The Sézary cells as seen in the peripheral blood show complex nuclear folding and periodic acid Shiff-positive vacuolization. Caution must be exercised, however, as small numbers of similar cells may be seen in patients with extensive benign inflammatory dermatoses.[44]

Malignant Lymphomas of True Histiocytic Origin

As noted previously, "histiocytic" lymphoma is usually a misnomer, the overwhelming majority of cases arising from transformed lymphoid cells. The only malignant lymphoma of unequivocal true histiocytic or macrophage origin is malignant histiocytosis (histiocytic medullary reticulosis of Robb-Smith).[21] This is a diffuse proliferation of malignant histiocytes usually associated with hepatosplenomegaly and consumptive cytopenias.[49] The occasional cases of large cell lymphoma with histiocytic markers probably represent tumoral examples of this disease. The true histiocytic nature of the malignant cells in malignant histiocytosis is suggested by the observation of in vivo erythrophagocytosis.[49] Marker studies of histiocytes demonstrate receptors for complement, high content of acid hydrolases, phagocytosis of latex particles and sensitized erythrocytes and cytoplasmic muramidase.[1] Demonstration of the latter by immunoperoxidase on fixed tissue sections may be of considerable diagnostic help in difficult cases.[50] The histiocytic nature of the proliferation is also supported by the pattern of spread, with selective involvement of normal his-

tiocyte domains: the sinusoids of the lymph nodes, liver and spleen. The condition was previously almost always progressive and fatal but now may be responsive to combination chemotherapy. A histologically similar but benign condition has been described in association with viral syndromes, particularly in immunosuppressed children.[51] The histiocytosis X complex (eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease) is also characterized by histiocytic proliferation, but the histiocytes are morphologically benign. The so-called soft tissue histiocytomas and fibrous histiocytomas are mesenchymal neoplasms probably unrelated to the monocyte-macrophage complex.

Hodgkin's Disease

The nature of the neoplastic proliferation in Hodgkin's disease remains unsettled. The mixed inflammatory infiltrate of plasma cells, lymphocytes, histiocytes and eosinophils suggested a reactive process to early observers. The clinical course and response to radiotherapy, however, is that of a malignant neoplasm. The diagnostic cell of Hodgkin's disease, the Reed-Sternberg cell, appears to be the neoplastic element. The accompanying inflammatory infiltrate may be an integral part of the neoplasm or more likely a host response. The nature of the Reed-Sternberg cell and its variants is unsettled. Similar binucleate cells with prominent nuclei may be seen in reactive lymph node conditions, such as infectious mononucleosis, and have been considered transformed lymphocytes. The defect in cellular immunity and tendency for paracortical involvement in Hodgkin's disease was for many years considered evidence of T cell origin. Immunoperoxidase study of tissue from Hodgkin's disease has shown surface and intracellular immunoglobulin associated with Reed-Sternberg cells.[52] However, the immunoglobulin is polyclonal and evidence suggests it is passively taken up by the Reed-Sternberg cells and not synthesized by them.[53] Recently, two groups have succeeded in establishing Hodgkin cells in tissue culture.[54,55] The cells morphologically resemble Reed-Sternberg cells and exhibit cytologic and cytogenetic evidence of malignancy. The cultured cells lack surface immunoglobulin and do not form E rosettes, but have receptors for complement and the Fc portion of IgG and secrete muramidase. These are features of the monocyte-macrophage complex and suggest that the Reed-Sternberg cell may be histiocytic in origin. However, uncultured Reed-Sternberg cells in tissue sections do not demonstrate immunoperoxidase staining for muramidase, and it is difficult to unequivocally establish that the cells observed in culture were actually derived from Reed-Sternberg cells. Indeed, one of these cell lines has subsequently been shown to be of nonhuman origin.[56] Thus, although the results of these tissue culture studies are exciting, the nature of the cellular proliferation in Hodgkin's disease remains unsettled.

Conclusions

Analysis of cell surface markers has provided enormous insight into the ontogeny of the immune system and the nature of the neoplastic proliferations derived from them—the malignant lymphomas. The development of new marker systems, including the hybridoma-derived monoclonal antibodies, promises to extend greatly our ability to discriminate classes of normal and neoplastic lymphoid cells. In the future, application of cell surface marker studies to the study of the lymphomas should continue to advance our ability to diagnose, classify and manage these conditions.

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Malaria: Immunity and Prospects for Vaccination

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Malaria infections elicit a complex chain of cellular events which can, in some instances, lead to a state of immunity. Although there is strong evidence that a collaboration between specific antibodies and activated macrophages plays the central effector role in malaria immunity, alternative interpretations are possible. It is, for example, not known which malarial antigens are essential for triggering the critical effector functions and how these antigens are presented to the immune system. Under these circumstances, it is not surprising that the search for a vaccine against malaria has used rather empirical methods. Three invasive stages of the parasite (merozoites, sporozoites and gametes) have so far shown a potential efficiency in inducing protection in experimental models, but there is much to be done before vaccination can be an effective tool in malaria control.

MALARIA TODAY remains the most lethal of all human parasitic diseases. The global eradication measures, based upon the use of insecticides and chemotherapy, have greatly reduced its incidence, but administrative and financial problems, aggravated by the spread of insecticide resistant mosquitoes and drug resistant parasites, have reversed the gains in some areas, particularly in South East Asia. In Sri Lanka, for example, the incidence of malaria was reduced to less than 1,000 cases per annum in 1965, but had reverted to pre-eradication levels in 1976 (almost 1 million new cases reported).[1] With the realization that the present methods for malaria control are expensive and no longer adequate in some areas of the world, new tools are being sought and vaccination against malaria, which was considered impractical by most scientists a decade ago, is now being reevaluated.

The general features of immunity to malaria have been extensively reviewed elsewhere[2-6] and it appears that a variety of immune responses are elicited during the course of malaria infection: a great variety of antibodies are produced and there is a considerable stimulation of nonspecific reticuloendothelial functions. Nevertheless, the development of resistance in humans is so slow that in endemic areas many children may be intermittently ill for a number of years before any sign of resistance appears and many die before they have any resistance at all. The critical questions are the following: Why does protective immunity develop so slowly in natural infections? Which immune responses are protective and which are useless or even harmful? Could a vaccine achieve

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ABBREVIATIONS USED IN TEXT

ADCC = antibody-dependent cytotoxic T cells
DNP = dinitrophenyl
EE = exo-erythrocytic
FCA = Freund's complete adjuvant
HRP = histidine-rich polypeptide
IMP = intramembranous particles
LAF = lymphocyte-activating factor
MDP = muramyldipeptide
MHC = major histocompatibility (antigen)
MIF = migration inhibition factor
NK = natural killer (cells)
TNP = trinitrophenyl
SRBC = sheep erythrocytes

protection more easily than the natural course of infection?

In this paper, I will consider the repertoire of immune responses that could be involved in promoting or inhibiting the development of resistance to malaria and examine the theoretical and practical problems that still remain to be solved before a vaccine against malaria can become a practical tool in the control of this disease.

Life Cycle of Plasmodium and Potential Points of Attack

There are four species that cause human malaria, *Plasmodium falciparum, P vivax, P ovale* and *P malariae,* each with a characteristic course of infection and pattern of disease.[7] However, most of the mortality associated with malaria is caused by *P falciparum* and it is against this infection that a vaccine is most urgently needed.

Much of the present knowledge concerning malaria in man has been derived from field studies and from controlled infections in neurosyphilitic patients and prisoner volunteers. Candidate vaccines, however, will have to be tested initially in animal models. Some New World monkeys—particularly owl monkeys *(Aotus trivirgatus)*[8] and squirrel monkeys *(Saimiri sciureus)*[9]—are susceptible to *P falciparum,* but these animals are limited in numbers and the course of infection differs from that in humans. Knowledge about malaria is derived largely from experimental studies carried out on laboratory animals infected with nonhuman malaria parasites. The organisms most commonly used for this purpose are *P berghei, P yoelii, P vinckei* and *P chabaudi,* which infect laboratory rodents, *P gallinaceum* and *P lophurae,* which infect chickens and ducks, and *P knowlesi,* which infects rhesus monkeys.[10] Each of these models presents specific advantages. It is worth mentioning here that none of these experimental models is a natural host-parasite combination (for example, *P berghei* is a parasite of an African rodent, *Grammomys surdaster,* adapted to grow in laboratory rodents) and that the criticism of possible irrelevance, which is sometimes leveled at *P falciparum* infection in nonhuman hosts, applies to all the common experimental models available.

The typical life cycle of mammalian *Plasmodium* sp is briefly the following (Figure 1): sporozoites are inoculated into the skin by infected anopheline mosquitoes and rapidly localize in the liver where they invade parenchymal cells. Inside these cells, each sporozoite develops into a schizont which will eventually liberate up to 20,000 individual merozoites capable of invading erythrocytes. Within the erythrocyte, the parasite divides and releases 6 to 20 merozoites which in turn can

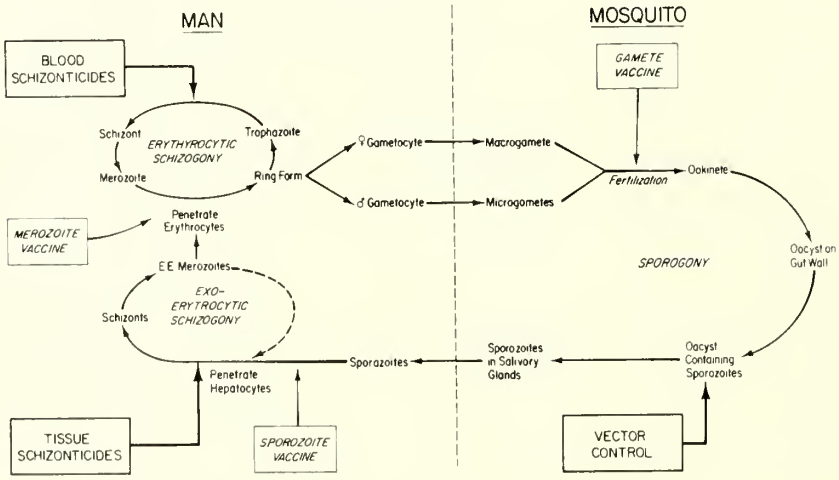

Figure 1.—Life cycle of malaria parasites showing the different points of attack either by classical control methods (chemotherapy and insecticides) or by vaccination.

invade new erythrocytes. In the course of this erythrocytic schizogony, a percentage of asexual parasites will develop into gametocytes which, when taken up by a mosquito, will transform into gametes. Fertilization occurs when a male microgamete penetrates into a female macrogamete. The ookinete that is produced migrates to the gut wall of the insect vector and develops into an oocyst. At the end of its development, each oocyst contains about 10,000 immature sporozoites, which mature and become infective in the process of their migration towards the salivary glands of the mosquito.

The malaria parasite is, therefore, intracellular during most of its life cycle, but is exposed to the extracellular space each time it invades a new host cell and during fertilization. The invasive forms are highly differentiated and equipped to invade only a specific cell type. Due to their extracellular nature, these invasive forms are the most obvious targets for an immunological attack (Figure 1). Once the parasite is intracellular, it is virtually invisible to the immune system and, given that it can resist the natural killing mechanisms of the host cell (which are negligible in erythrocytes), it cannot be recognized or destroyed by effector cells, unless the surface of the infected cell is modified by the parasite.

Critical Malarial Antigens

In the course of malaria infection, the immune system is exposed to a range of parasitic antigens, but, although their respective role in the induction of protection is unknown, some of these antigens could play a more critical role than others because of their location either on the surface of infected cells or invasive forms or their presence as soluble antigens in the bloodstream.

Surface of Invasive Forms

The surface of merozoites is covered by a thick filamentous coat which is morphologically similar to that described in trypanosomes and is believed to be involved in the recognition-adherence which will eventually lead to erythrocyte invasion; the coat appears to be shed from the surface when the merozoite enters into the red cell.[11,12] The surface coat has been described as T-shaped bristles mounted perpendicularly to the cell membrane and has been shown to stain strongly with ethanolic phosphotungstic acid, to bind ruthenium red, alcian blue-lanthanum nitrate and cationized ferritin, and to be removed by proteases (criteria which suggest a glycoprotein nature), but does not bind any of the usual lectins.[13,14] The coat is present on the surface of merozoites before the mature schizont (segmenter) ruptures, but it becomes thicker after the merozoites are released into the circulation.[15] By analogy with trypanosomes, some authors have suggested that the coat could consist of a single glycoprotein which would, as in trypanosomes,[16] be involved in immune evasion by a process of antigenic variation,[17] but this attractive hypothesis has not yet been confirmed experimentally.

In *P knowlesi* infections, merozoites are agglutinated by immune serum in vitro and this effect is associated with reduced in vitro invasion.[15] The inhibitory action is concentrated in the IgM and the IgG fractions of the immune serum—or the $F(ab')_2$ fragments—and is independent of complement.[18] Although reinvasion inhibition is more pronounced with homologous than heterologous strains, it is not clear whether variant specific antibodies are directly involved. The fact that variant specific sera can be used to separate merozoites from schizont-infected cells by differential agglutination suggests that these antibodies do not take part in merozoite agglutination and in vitro invasion inhibition.[19] Moreover, there appears to be a certain degree of correlation between clinical immunity and in vitro inhibition of invasion[20,21] which further suggests that antibodies directed against surface components of merozoites may play a critical role in protection. Further, the binding of fluorescein-labeled antibodies to the surface of *P berghei* merozoites in vitro has been shown to be correlate with passive transfer of antibodies and protection.[22]

Recent experiments using monoclonal antibodies have shown in *P yoelii* that antibodies directed against the merozoite surface could be used to block the entry of the parasite into erythrocytes in vivo, whereas antibodies directed against other malarial antigens had no effect.[23] Little is known about the surface of exoerythrocytic (EE) merozoites (that is, merozoites released by liver schizonts) and whether these forms are identical to erythrocytic merozoites. In infections with the avian parasite *P fallax*, a difference between these two forms has been shown to exist: when turkeys are infected with EE forms and treated with chloroquine to suppress erythrocytic development, their sera can be used to passively protect other turkeys against EE forms (that is, 90 percent of EE merozoites are de-

stroyed), but has no effect on the development of homologous erythroeytic stages.[24]

The fact that the surfaee antigens of different invasive forms are stage-specific is not surprising, considering that they are equipped to recognize and invade such different eells. Antibodies against the surface of sporozoites can be detected by using the circum-sporozoite precipitation method[25]: in presence of antibodies the formation of a precipitate around the terminal end of the sporozoite can be observed using phase-contrast microscopy. The surface of sporozoites not only differs antigenically from other stages of the same parasite, but also differs from that of sporozoites of unrelated species.[26] Furthermore, the surface antigens responsible for this precipitation change during sporozoite maturation: antiserum prepared against salivary gland forms does not eross-react with oocyst (immature) forms. When sporozoites of *P berghei* are ineubated in immune serum, they rapidly lose their infeetivity. There is, however, little correlation between this in vitro sporozoite neutralizing activity and protection against sporozoite challenge.[27] The eritical question so far as surface antigens are concerned is the following: does a single moleeular species cover the entire organism or is there a mosaic of antigens? In the ease of *P berghei* sporozoites, a single protein, 44,000 MW, seems to account for all three biological activities: a monoclonal antibody directed against this protein (Pb44) produces a circum-sporozoite preeipitation and in vitro neutralization, and can be used to passively protect against sporozoite challenge in mice.[28,29]

Membrane-Associated Antigens

The membrane of malaria-infected erythrocytes undergoes dramatic changes as the parasite grows from the ring to the schizont stage. Surface labeling techniques have revealed both the loss of some components of normal membranes and the acquisition of others which were not present on the surface of normal cells.[30-33] The appearance of parasite-speeific components on the surface of infected erythrocytes is still controversial. *P knowlesi* schizont-infected erythrocytes can be agglutinated by immune serum[34] and this agglutination has been shown to be strain-specific and submitted to a pattern of antigenic variation.[35] The variant antigens, however, have not yet been ehemieally defined and the evidence of their parasitie nature remains circumstantial. On the other hand, at least seven new proteins have been detected by immunochemical methods on ghosts of infeeted erythrocytes prepared by nitrogen cavitation.[36-39] There is no doubt about the parasitic nature of these proteins (they can be metabolically pulse-labeled, while erythrocyte eomponents cannot), but their localization on the outer membrane of infected erythrocytes, rather than on the parasitophorous vacuole or the parasite membrane, has not yet been unambiguously demonstrated.

With *P falciparum* and eertain other primate malaria parasites, electron microscopic studies have shown the presence of dense areas protruding on the surface of infected erythrocytes,[39] whieh are believed to be responsible for the sequestration of schizont-infected cells in capillaries through adhesion to the endothelial epithelium. These structures, called knobs, may fail to appear on the host eell surfaee when the parasite has been submitted to long-term in vitro cultivation and knobless strains have been shown to lack a 80,000 MW protein.[41] Knobs can induce an antibody response in immune animals[42] and there is evidence suggesting that the immune reeognition of surface determinants present on infected erythrocytes can be strain specific.[43] The hypothesis of knobs being parasitic material inserted into the erythrocyte membrane would be strengthened if a positive correlation among morphological, biochemieal and immunological data were to be shown. Results of reeent immunochemical studies have indicated that such a correlation might prove difficult to establish, in view of the instability and "stickiness" of the knob material.[41,44]

In *P berghei,* a parasite which preferentially invades retieuloeytes, neither knobs nor variant-antigens have been detected on the surface of infeeted cells, but the binding of specific antibodies could be an indication of the existence of parasitic antigens on the surface of infeeted reticulocytes. Such binding has been visualized by immunofluorescence using monoclonal antibodies,[23] by immunoperoxidase staining[45] and by antitrinitrophenyl (anti-TNP) plaque formation.[46,47] These results must, however, be interpreted with caution beeause infected reticulocytes have been shown to bind nonspecifically a variety of serum proteins[48]; modified reticulocyte components, rather than parasite antigens, eould be responsible both for the induction of specific antibodies and their binding.

No surfaee alteration which might suggest the presence of parasitic antigen has been described in malaria-infected hepatocytes. Such studies are

technically difficult: this stage has not yet been adequately maintained in vitro and, in vivo the percentage of infected cells is very low, even after a massive injection of infective sporozoites. Malarial antigens associated with the surface of cells harboring EE forms could, however, play an immunological role, particularly in parasite infection where there is a long-lasting exo-erythrocytic development (for example, *P malariae*) or where EE forms are cyclic. The latter is the case in avian malaria, where EE forms occur in various cells and can be maintained in vitro (for example, in turkey brain cells).[49,50]

The parasitophorous vacuole membrane is perhaps the membrane of erythrocytic origin most likely to carry membrane-associated malarial antigens because of its close contact with and its role in the metabolism of the malaria parasite. Its formation is induced by the release of rhoptry material from the apical end of the invading merozoite[12,51] and it surrounds the parasite throughout its development. Shortly after its formation, this membrane has virtually no intramembranous particles (IMP)[52] and histochemical studies of enzyme activity have shown that ATPase and NADH (nicotinamide adenine dinucleotide, reduced) oxidase activity were found on the same side as on the erythrocyte outer membrane, rather than being reversed as would be expected in an invaginated erythrocyte membrane.[53] When the parasite has reached the schizont stage, numerous IMP are found in the parasitophorous vacuole membrane,[52] suggesting either that some parasite material has been inserted or that IMP from the outer erythrocyte membrane have moved to the interior, thus implying an intermittent continuity between these membranes, as well as a disruption of the spectrin network (spectrin does not normally allow lateral mobility of IMP). The immunological importance of the parasitophorous vacuole membrane is not known: this membrane is not exposed to the outside during the growth of the parasite, but is released in the form of vesicles at the time of schizogony. Other parasite material released in the circulation during the schizogony-reinvasion process includes the residual body (that is, digestive vacuole of the parasite containing the pigment) and the surface coat of merozoites. Most of this material is rapidly taken up by phagocytic cells and therefore could be involved with or interfere with the antigen presentation function of macrophages which, in the final analysis, represents the most efficient mechanism of recognition. The recognition by lymphocytes of macrophage-processed malarial antigen has been shown in vitro.[54]

Soluble Circulating Antigens

Soluble circulating antigens have been described in infections with *P knowlesi, P lophurae, P gallinaceum, P berghei* and *P falciparum*.[55-59] The exact origin, nature and significance of these various antigens is not clear. In *P falciparum* infections, heat-resistant soluble (S)-antigens have been described that are parasite strain specific—that is, the same S-antigens are always found in a given laboratory strain, whether it is maintained in an owl monkey, a squirrel monkey or in vitro.[60] This observation, in view of the variety of S-antigens found in clinical cases in a limited geographical area,[61] suggests that the strain complexity of human malaria is much greater than is usually believed. Soluble antigens are usually considered to have a detrimental effect on the development of resistance against malaria: they bind specific antibodies and form circulating immune complexes, which can cause a range of immunopathological complications.[62] Another possibility is that these soluble antigens are partially degraded malarial antigens (for example, a polysaccharide chain of a glycoprotein) which, although they are no longer immunogenic, can block the immune response by inactivating or removing specific antibodies from the circulation[63] or by inducing immune suppression.

Repertoire of Immune Responses to Malaria

The respective roles of the various components of the immune system in the development of an acquired immunity to malaria are still unclear, but all the available data point towards a complex mechanism involving both humoral and cell-mediated factors. What follows is an attempt to dissect this mechanism and examine how the different effectors might interact.

Innate Resistance and Natural Killer Cells

Malaria merozoites only can invade the erythrocytes of certain host species and within these species they usually have a preference for a given subpopulation of red cells. In the case of *P knowlesi* and *P vivax*, erythrocyte preference has been pinpointed to a defined erythrocyte receptor which is somehow associated with the presence of the Duffy blood group.[64] A second level of resistance occurs inside the erythrocyte where

cytoplasmic components can interfere with malarial growth: *P falciparum* has a preference for young erythrocytes[65] and it has been shown that erythrocytes containing certain abnormal hemoglobins are less favorable for its development.[66] In many circumstances where a genetically controlled resistance to infection has been detected, a linkage can be shown with a major histocompatibility (MHC) antigen. In *P falciparum* infections, such a linkage has so far not been found, although HLA-typing has been used in large scale epidemiological studies. However, a hint of evidence that that MHC genes may be important in malaria comes from a study of HLA phenotypes in four Sardinian villages: an excess of HLA-A_2 and HLA-B_{17} genes was noted in the people in lowland villages, which have been exposed to malaria for the last two centuries, while no excess of any HLA genes could be found in the inhabitants of highland villages unexposed to malaria.[67] The higher frequency of antibody against malaria in these same two HLA phenotypes in Tanzania suggests that they are indeed associated with some resistance against malaria.[68]

In rodent malaria, where experiments can now be carried out in inbred strains of mice having a precise H-2 background, all attempts to show a relationship between resistance and MHC factors have so far been disappointing. A variation in susceptibility of different strains of mice to rodent malaria does, however, exist[64] and it has recently been suggested that this variation could be related to a variable activity or levels of natural killer (NK) cells. Mice of strain A, which have a low NK activity, are highly susceptible to *P chabaudi* and do not have any great increase of NK activity (as measured by lysis of target tumor cells in vitro) at the peak of parasitemia, whereas strains which are less susceptible to this parasite (for example, CBA or C57B1) show a considerable increase of NK activity during malaria infection.[69] It is possible that NK cells are involved at a more specific level of resistance, particularly as these cells are stimulated by various substances including interferon. The latter has been shown to be present at high titers in the serum of malaria infected animals, probably under the influence of a high level of macrophage activation (see below). It could be suggested, in this context, that the nonspecific protection against *P berghei* in mice produced by the injection of BCG (bacillus Calmette-Guerin)[70] might be obtained through this pathway.

The Role of T Cells

There is abundant evidence that T cells play a role in the acquired immunity against malaria. In the case of rodent malaria, thymectomy of neonatal rats or treatment with antithymocyte serum causes a pronounced exacerbation of *P berghei* infection[71,72] and a lethal infection with an otherwise mild strain of *P yoelii* develops in athymic nude mice.[73,74] Resistance has been adoptively transferred with immune spleen cells,[75,76] but little information is available on the transfer of purified cell populations. There has been no study of the kinetics of the different T lymphocyte subsets in the course of malaria infection, but an overall decrease of circulating T cells has been reported both in patients with *P falciparum*[77] and in rodent models[78] and seems to be related to a sequestration of these cells by the spleen.

The role of helper T cells has been explored by using parasites or parasitized cells as carrier for TNP and detecting the anti-TNP plaque forming response of the spleen at different stages of malaria infection or after immunization.[46] These studies showed little or no correlation between helper T cell response and protection against malaria suggesting that T cell functions other than the regulation of antibody formation are involved. The same is suggested by experiments using B-deficient mice which were drug-rescued from an otherwise lethal infection with *P yoelii:* these mice had a certain degree of resistance against the same strain despite the lack of detectable antibody.[79]

Direct killing of parasitized cells by cytotoxic T cells has been reported in *P berghei* infections with an in vitro assay where the lysis of infected erythrocytes was shown by chromium 51 release,[80] but the interpretation of this result is difficult, particularly in view of the spontaneous fragility of mouse erythrocytes in vitro. Such killing could not be accomplished in a similar study using *P knowlesi.*[81] Nevertheless, the increase in killer cell activity (associated with a general depletion of T cells and B cells) has been reported both in children with acute *P falciparum* infections[82] and in rodent malaria models[83] and suggests that antibody-dependent cytotoxic T cells (ADCC) could participate in the protective response to malaria.

There is ample clinical and experimental evidence that acute malaria produces a temporary immunosuppression[84,85] which might account for the greater severity of intercurrent infections (such as measles, respiratory infection and gas-

troenteritis) in children with malaria. The immune response to many antigens, including heterologous erythrocytes, human immunoglobulin, tetanus toxoid, *Salmonella typhimurium* and various murine viruses, is suppressed while the response to other antigens is normal (keyhole limpet hemocyanin is an example). The mechanism of this immunosuppression is not known, but there is little or no evidence to suggest a suppressor T cell involvement. In mice infected with *P berghei,* there is an intense nonspecific immunosuppression which affects both T and B functions, but when spleen cells from infected mice are mixed with normal spleen cells there is no reduction of phytohemagglutinin (PHA)-induced transformation.[6] Similarly, a normal response to PHA (1 gram per ml) was obtained with peripheral lymphocytes from children with acute falciparum malaria,[86] but with lower doses of PHA (0.1 gram per ml) a decreased response was noted, particularly in a case where chronic *P malariae* infection was associated.[87] On the other hand, the peripheral blood lymphocytes of *Aotus trivirgatus* showed a reduced response to various mitogens at the acute stage of *P falciparum* infection[88] and, when the serum of such animals was added to normal owl monkey or human lymphocytes, a decreased mitogen response was also observed.[89] An inhibitor of lymphocyte proliferation could not, however, be found in sera of patients with falciparum malaria.[90]

The function of T cells in promoting macrophage activation through the secretion of lymphokines has not been examined thoroughly in malaria. In *P yoelii* infected mice the study of macrophage kinetics suggests that monocytes leave the bone marrow and accumulate in the liver and spleen just before recovery.[6] This migration occurs more rapidly in specifically vaccinated mice and these newly arrived macrophages appear to be highly activated but it is not known whether they actually destroy the parasites. The specific accumulation of monocytes in the spleen seems to be under the influence of a 80,000 MW chemotactic factor secreted by the spleen cells throughout malaria infection and which can be detected as early as four hours after infection—that is, about 48 hours before any detectable increase of splenic macrophages.[91] Moreover, the role of T cells in the recruitment and activation of macrophages has been demonstrated in T deficient (nu/nu) mice, which show little splenomegaly and no enhancement of phagocytosis during malaria infection, whereas B deficient mice behave normally.[92] The disappearance of macrophages from the peritoneal cavity and the detection of a macrophage migration inhibition factor (MIF) in spleen cells of acutely infected mice points in the same direction.[93] Delayed hypersensitivity, as measured by the homing of labeled bone marrow cells to the ear after local challenge with the antigen—that is, *P yoelii*-infected red cells—is greatly increased in specifically vaccinated mice, particularly in conditions which lead to protection.[94] These results suggest the existence of a T cell function with protective value, but, at the same time, they indicate that T cells alone are not responsible for protection.

The Role of Macrophages

The role of macrophages in malaria was recognized 40 years ago by pathologists, who showed an increased number of macrophages in the spleen, liver and bone marrow of infected animals. During the parasitic crisis (when parasitemia starts to decrease under the influence of acquired immunity) there is a considerable increase in phagocytosis of malaria parasites, infected erythrocytes and malarial debris (particularly pigment).[95] In rodent malaria, where the phagocytic activity of splenic macrophages can be 20- to 50-fold greater than that of normal macrophages,[4] there is an increased uptake of normal as well as infected red cells.[96] This increase in phagocytic activity has been linked both to a specific activation of macrophages and to humoral factors, particularly opsonizing antibodies, which act synergistically with macrophages to enhance the destruction of the parasites.[97-99] The enhancement of phagocytic activity, however, does not always last throughout the infection and can, for unknown reasons, become normal or subnormal before there is any reduction in the level of parasitemia, suggesting that, at this stage of infection, phagocytic activity is no longer indispensable for the development of functional immunity.[100]

Activation of macrophages produces a variety of substances which can trigger other immune functions. Among these, interferon production has been demonstrated,[101] and the presence of interferon has been related to resistance, at least against sporozoite infection[102]; the role of interferon in increasing NK activity has been suggested as a possible effector mechanism.[69] In this context, the function of macrophages in immunity has recently been analyzed with agents known to inhibit or stimulate macrophage activity in vivo (silica

and *Corynebacterium parvum,* respectively): in normal mice, administration of silica accelerated the appearance of parasites in the blood and *C parvum* delayed it, whereas in vaccinated mice, the clearance of parasitemia was accelerated by silica and delayed by *C parvum*. These results suggest that macrophages, especially if activated, could inhibit the development of sterilizing immunity, apparently by inhibition of the IgG response.[103] This paradoxical effect might be related to a reduced secretion of lymphocyte-activating factor (LAF)[104] and the production of suppressor factors by adherent spleen cells of malaria-infected mice.[105] The helper function of macrophages appears to be normal at the beginning of infection, but is severely altered later.[106,107] This has been shown in a study of in vitro antibody formation in response to sheep erythrocytes (SRBC) and dinitrophenyl (DNP)-Ficoll by adherent spleen cells from infected and normal mice; between days 2 and 4 of a *P yoelii* infection, the antibody response to both antigens was enhanced and a pronounced reduction was observed, between days 8 and 21, only in the case of SRBC, while the response to DNP-Ficoll (which is macrophage-independent) was normal.[107]

The Role of Antibodies

The role of antibodies in resistance against malaria has been studied by three different approaches: the passive transfer of immune sera, the in vitro effect of immune serum on isolated parasites and the infection of B deficient animals.

Passive transfer experiments show that antibodies merely cause a transient reduction of the parasitemia.[108-112] This reduction can be sufficient to allow the host to develop an effective response and thus recover from an otherwise fatal infection. In *P falciparum* infections, large amounts of IgG from immune adults (doses equivalent to 10 percent to 20 percent of the recipient's own IgG) reduced the parasitemia to undetectable levels in heavily infected children,[109] but this protection was of short duration. The relative resistance of infants in hyperendemic areas could be explained by the passive transfer of antibodies from the mother, although other factors, such as the presence of fetal hemoglobin or the age of erythrocytes[113] could be involved. The variability observed in passive transfer experiments, particularly in rodent malaria, seems to be related to the doses of immune serum administered as well as the variable quality of these sera. The fact that large amounts of serum from recently recovered mice does not confer any protection against *P yoelii*[114] might be due to the persistence in convalescent serum (as opposed to hyperimmune serum) of soluble malarial antigens and immunosuppressive factors, the role of which has been discussed above. The protective effect of monoclonal antibodies directed against the surface components of merozoites or sporozoites of *P berghei*[23,29] clearly supports such a view. The activity of hyperimmune serum could partially be related to opsonization,[99,115] particularly as passive serum transfer is more effective in intact than in splenectomized recipients.[116-117] In *P knowlesi* infections, when antiserum against a given variant population is transferred to an animal infected with this variant, a transient reduction of parasitemia is obtained and a new variant population is induced, which, being no longer controlled by the antiserum, produces a lethal infection.[118] Moreover, variant-specific antibodies have different kinetics than the antibodies responsible for opsonization, which suggests that they represent different entities.[119] The transfer of T depleted immune spleen cells confers the same degree of protection to *P berghei* as spleen cells not T depleted, suggesting that B cells alone were responsible for the protective effect.[120] However, contradictory results from similar experiments[121] and the large body of data concerning the involvement of T cells do not favor such an interpretation.

It has been reported that immune sera can affect sporozoites, merozoites and gametes in vitro. The sporozoite neutralizing test and the circum-sporozoite test can be used to demonstrate antisporozoite activity of immune sera. The correlation of these assays with protection is generally considered to be poor,[27] although the results obtained with monoclonal antibodies suggest that this poor correlation might be related to other factors.[28] The effect of immune serum on merozoites can be measured with an in vitro reinvasion assay and inhibitory activity as has been demonstrated with *P falciparum* and *P knowlesi*. In the latter case, the sera from immune animals inhibit reinvasion by producing an agglutination of merozoites[15-18]: this assay was found to correlate well with the results of transfer experiments,[122] but not always with functional immunity.[123]

An interesting observation has been made by using frozen blood samples taken from patients infected with *P falciparum* in The Gambia. In vitro reinvasion was tested in the presence of

homologous sera (that is, sera taken from the same patient at later stages of infection or after recovery) and heterologous sera. Inhibitory titers were always higher with homologous sera, probably in connection with the above-mentioned strain complexity of *P falciparum*.[124] The sera from patients who have recovered from falciparum malaria have no effect on either bloodstream gametocytes[109] or on the infectivity of these sexual forms for the mosquito vector.[125] In some simian malaria, however, a striking contrast between the high number of gametocytes present in the bloodstream on day 14 of infection and the failure to produce any infection in the vector, has been reported.[126] Furthermore, in chickens immunized against gametes of *P gallinaceum*, the infectivity of gametes can be completely suppressed in vivo, and in vitro the immune serum has been shown to block fertilization and ookinete formation. Two types of interactions between immune serum and gametes have been described: a surface *fixation* reaction, where small numbers of gametes are loosely attached together, and an agglutination reaction, where large numbers of gametes are clumped. A correlation between these in vitro assays and the suppression of infectivity was observed only in the case of the agglutination reaction.[127] With monoclonal antibodies directed against surface antigens of gametes, a surface fixation reaction can be observed, but agglutination (and suppression of infectivity) is only obtained by mixing monoclonal antibodies against two different surface components.[128] The use of B deficient animals, whether bursectomized chickens[129] or mice rendered deficient by treatment from birth with anti-μ serum,[74,79] gives further evidence of the role of antibodies in acquired immunity to malaria, and shows that a collaboration between T cells and B cells is necessary for maximum protection.

Another aspect of the antibody response in malaria infections is that considerably more IgG is produced than can be accounted for by specific antimalarial antibodies.[130] It has been shown that a polyclonal stimulation by malaria mitogens could, at least to some extent, explain this effect.[131] The nonspecific polyclonal B cell activation, which occurs during the course of malaria infections, does not result from a direct stimulation of B lymphocytes by mitogenic factors but has been shown to be T dependent. The following chain of events has been proposed: T cell mitogens, which are produced either by the parasite or by the macrophages of infected animals, activate T cells, which in turn contribute to a B cell activation through a T helper effect[17,132]; the detailed mechanisms of this phenomenon are not yet fully understood.

The Role of Complement

A depletion of various complement components, particularly C3, has been reported to occur during the course of infection by various malaria parasites.[133-136] In the synchronous *P knowlesi* infection, the reduction of complement activity paralleled the peak of schizogony and was therefore attributed to the release of free parasites into the bloodstream.[137] On the other hand, the peak of schizogony corresponds to the maximum release of circulating antigens and therefore of the formation of immune complexes. It could be argued that the solubilization of immune complexes, a function of the alternative pathway, might be responsible for the decreased level of complement. Interestingly, both the presence of immune complexes and of the complement cleavage product C3b are known to activate macrophages and could, thus, play a role in triggering the chain of events that leads to protection. The nonspecific protection against malaria conferred by *C parvum*, an agent that activates the complement alternative pathway, could be related to this mechanism.[138] No direct complement-mediated cytotoxicity has been reported.

Overall Interactions

Assuming that the results obtained in the various experimental systems can be generalized, the following chain of events is suggested to explain the development of a functional immunity in malaria (Figure 2): (1) the recognition of the various malarial antigens (that is, surface of invasive forms, host-cell membrane associated antigens, soluble circulating antigens and antigens presented by macrophages) involves different types of T cells (for example, helper T cells are more likely to recognize malarial antigen associated with Ia antigens on the surface of macrophages rather than free antigen, while suppressor T cells are more likely to recognize free antigen); (2) these T cells, in turn, activate various effector cells, particularly B cells and macrophages; (3) the products of these effector cells will either react directly with the parasite (for example, invasion inhibition by antibodies or through the effect of interferon on host cells) or can act synergistically

with another effector cell or product to cause a cytotoxic effect (for example, opsonization by macrophages or ADCC) or can stimulate other functions (for example, interferon activation of NK cells), and (4) this chain of events is regulated in various ways by the parasite: circulating malaria antigens bind antibodies (thereby reducing serum antibody levels against the parasites). Soluble antigens also form circulating immune complexes, which in turn activate complement pathways and macrophages. Activated macrophages produce various factors, some of which interact with T cell functions and secondarily influence antibody formation. During the acute phase of infection, suppressive factors are produced that interfere with macrophage antigen-processing functions and cause negative feedback inhibition of T cell functions. At the same time, mitogens are secreted which *sidetrack* the immune system into a polyclonal B cell activation, probably through a T helper effect. Immunopathological side effects can be produced by many of these mechanisms, but their role in protection is not known.

Which Vaccine?

In view of the complexity of the immune response induced by natural malarial infections, it is possible to imagine that effective protection could be obtained more easily by a mechanism that stimulates only one kind of effector cell and, therefore, bypasses all the detrimental regulatory factors. The choice of immunogen is obviously critical but, in the present state of our knowledge, it is not possible to decide which particular antigen, if any, would make the best vaccine. The current views of malaria vaccination[3,24,138] are the following: (1) the best protection is obtained by a low level infection which will lead to a state of premunition; (2) only live, attenuated parasites (such as irradiated sporozoites) can produce complete protection; (3) killed parasites are generally only efficient in the presence of adjuvants and, at best, only achieve a partial stage-specific protection, which allows the host to survive a mild initial infection and, thus, built-up premunition; (4) parasite extracts or semipurified parasite extracts are generally ineffective even in the presence of adjuvants; (5) purified malarial antigens might succeed where parasite extracts have failed; (6) an interruption of the life cycle by interaction of invasion-blocking antibodies with invasive forms is generally considered to be the most hopeful line of investigation; finally, (7) interruption of transmission can be achieved without protecting the immunized recipient (for example, gamete vaccine).

The search for a malarial antigen that can induce an effective immunity has recently taken two different directions: the purification of stage-specific antigens and the preparation of antibodies with specific inhibitory activity. The purification

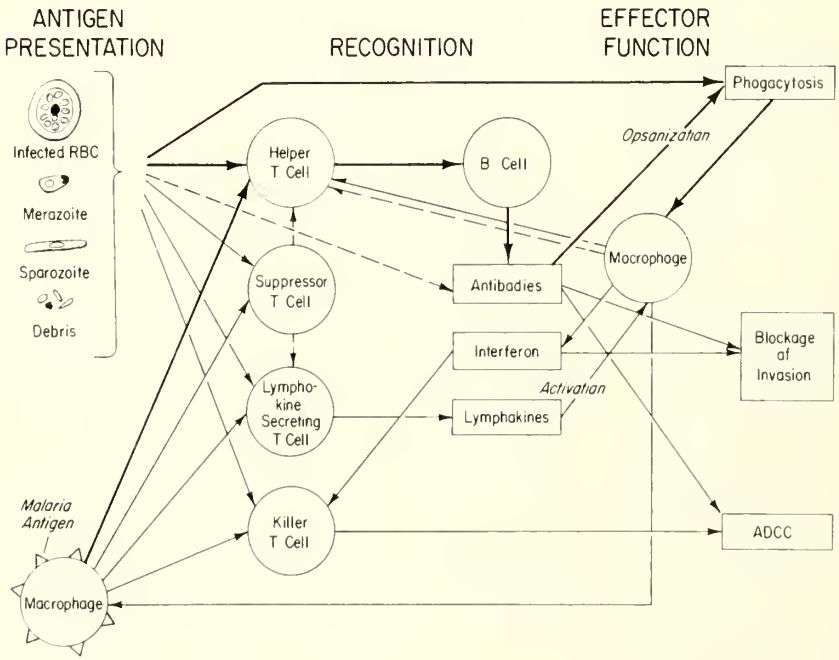

Figure 2.—Overall interactions of the different components of the immune system in response to malaria infection.

ADCC = antibody-dependent cytotoxic T cells, RBC = red blood cell (erythrocyte)

of stage-specific parasite populations is usually necessary before stage-specific antigens can be isolated. Merozoites can be separated from blood cells by using different methods: agglutination with lectins or antibodies,[19,140] filtration through a small pore-size cell-sieve,[141] elution from affinity columns[142,143] or centrifugation of in vitro culture supernatants.[144] None of these methods is perfect and the merozoite preparations obtained are always somewhat contaminated with host cell material. Nevertheless, such merozoite preparations have been used for vaccination experiments with the following results: merozoites of *P knowlesi,* when given with Freund's complete adjuvant (FCA), gave a partial protection against challenge with erythrocytic stages of homologous and heterologous strains of *P knowlesi*[140,145] or against a sporozoite challenge[146]; the results obtained with other adjuvants (Freund's incomplete adjuvant with or without muramyldipeptide [MDP] derivatives, saponin) gave less consistent results.[147] Merozoites of *P falciparum* have been used to partially protect owl monkeys in conjunction with either FCA[142] or MDP derivatives.[148,149] In rodent malaria, most vaccination experiments using merozoites have given disappointing results.[3]

The purification of sporozoites requires the dissection of infected mosquito salivary glands followed by the separation of sporozoites and mosquito material by gradient centrifugation[150,152] or differential elution from lectin columns.[28] The contamination with mosquito material is generally considered to be less critical than the contamination with blood cell components, particularly as some kind of additional nonspecific protection can be conferred by mosquito extracts alone[153]: such sporozoite preparations have actually been used in preliminary clinical trials. Most of the work on sporozoite vaccination has been done in the rodent models, where irradiated sporozoites have been shown to produce a complete, sterile immunity in more than 90 percent of the immunized animals.[25] Moreover, sporozoite vaccines do not appear to require any adjuvants. Sporozoite vaccination in simian models[154,155] or in human volunteers[156,157] yields more variable results and is generally less efficient. The protection conferred by sporozoite vaccines is usually of short duration: three months or less.

Gametocytes can be purified by differential centrifugation[158] and gametes can be prepared by controlled gametogenesis in vitro followed by differential centrifugation to separate the extracellular gametes from blood cells and asexual parasites. Gamete vaccines have been explored in *P knowlesi, P gallinaceum* and *P berghei* with similar results: the vector infectivity of the blood of immunized animals could be totally suppressed by circulating antibodies. These antibodies are taken up in the blood meal and interact with the gametes as soon as they become extracellular in the mosquito gut and, thereby, prevent fertilization.[159-161]

A purified histidine-rich polypeptide (HRP), isolated from *P lophurae*-infected erythrocytes, and believed to represent rhoptry material,[162] has been used without any adjuvant to immunize ducks. A partial protection was obtained in most immunized animals—that is, a mild infection developed with an otherwise lethal parasite.[163] In this case, no preliminary separation of parasites from host cell material was necessary because of the peculiar chemical nature of this antigen (soluble in acetic acid). Unfortunately, this exciting result (the only circumstance where a purified antigen has protected against malaria) could not be reproduced in another laboratory using similar experimental conditions and somewhat larger groups of animals[164] and this obviously calls for further experimental data.

All these experiments suffer from one major drawback: the amount of parasite material necessary for immunization is considerable and the methods available for the production of such material are generally inadequate. Erythrocytic forms of *P falciparum* can be grown in vitro in fresh or outdated human red blood cell cultures[165] but the parasitemia obtained does not exceed 10 percent and parasites are usually asynchronous. Techniques have been developed to concentrate parasitized cells,[166,167] to obtain short-term synchronous cultures[168] and to induce the transformation of asexual stages into gametocytes,[169] but their yield is generally low. Parasite material obtained from infected experimental animals (for example, owl monkeys) or from human placenta in hyperendemic areas[170] has been used in preliminary studies, but cannot be considered as a suitable source of antigenic material for human vaccination. The situation is worse in the case of sporozoites because the sporogony cannot yet be achieved in vitro and salivary glands of infected mosquitoes still remain the exclusive source of parasite material. The case of histidine-rich protein, a potentially efficient malarial immunogen, is a good example of the present limitations of

malarial vaccines: 100 ml of infected duck blood containing approximately 100 percent schizont-infected cells (*P lophurae* produces synchronous infections) is necessary to prepare 2 ml of free parasites, which corresponds to 25 mg of HRP[171] and 2 mg of HRP is required to immunize a single duckling.[163] If the same material were to be prepared from *P falciparum* cultures, assuming that the cultures contain 10 percent asynchronous parasites and that *P falciparum* contains as much HRP as *P lophurae,* at least 6 liters of human blood, 3 liters of human serum and 30 liters of medium would be required to produce 25 mg of HRP. Obviously, the solution lies elsewhere than in the direct purification of antigens from malaria parasites. The DNA recombinant technology could, for example, be of value if the antigen desired for vaccination proved to be a short polypeptide chain. Chemical synthesis could be envisaged if the critical antigen were carbohydrate in nature.

The second approach for the recognition of vaccinating antigens is the use of specific antibodies with an inhibitory activity against one of the three invasive forms. This approach, which essentially uses the hybridoma technology for the production of monoclonal antibodies, has recently given encouraging results with all three invasive forms in rodent and in avian models[22,27,128] and should lead rapidly to the isolation of the relevant antigens. Furthermore, the possible use of anti-idiotype serum directed against such protective monoclonal antibodies could represent an alternative to vaccination with malarial antigens and bypass the difficult problems of antigen production.

Finally, two types of interaction between pharmacological agents and the immune system have to be considered. On the one hand, the treatment with antimalarial drugs can either impair the development of immunity by reducing the duration of antigen stimulation[172] or favor the development of immunity by reducing the level of parasitemia and, therefore, producing a more protracted course of infection. On the other hand, a variety of compounds can be used as immune adjuvants and all vaccination procedures using killed parasites have been shown to require some kind of adjuvant.[173] The role of these adjuvants is imperfectly known and it is likely that with a better understanding of the effectors of malaria immunity such empirical additives will no longer be required.

Conclusion

There is now a strong body of experimental data to suggest that malaria vaccines could provide a more solid immunity than the natural infection and could therefore prove to be a powerful tool in the fight against malaria. There is still a long way to go before trials of malaria vaccines can be envisaged in man; the problems in need of solution include the recognition and purification of suitable malarial antigens, the development of reliable in vitro tests to measure protective immunity and a better knowledge of strain complexity and possible cross-reactions between different strains. Moreover, if an effective vaccine against malaria were to become available, its application in the developing world would require massive international support and collaboration. Indeed, many of the available vaccines against infectious diseases are still not extensively used in the areas where they are most needed, because the affected nations cannot afford their purchase and do not have the medical infrastructure for their distribution.

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Refer to: Coleman DL: Smoke inhalation—Medical Staff Conference, University of California, San Francisco. West J Med 135:300-309, Oct 1981

Smoke Inhalation

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *At this time of year it is customary to invite our chief residents to present Medical Grand Rounds. This enables us to express publicly our appreciation for the superb leadership they have provided in our teaching and patient-care program. Dr. Diana Coleman has chosen the topic of smoke inhalation for discussion.*

Case Presentation

Dr. COLEMAN:† A 33-year-old, previously healthy man was admitted to hospital because of an inhalation injury sustained during a fire in his apartment. The patient had awakened to find his bedroom filled with smoke and his living room ablaze. He attempted to escape but was found semiconscious near the closed patio door in his bedroom. The patient was removed from the fire. Oxygen was administered by face mask, and he was brought to the emergency room approximately 20 minutes after being found.

In the emergency room, he was conscious, coughing up sooty material and complaining hoarsely of shortness of breath. Blood pressure was 110/70 mm of mercury, heart rate 130 beats per minute and respiratory rate 18 breaths per minute. There was no pulsus paradoxus. The skin was sooty but there were no cutaneous burns; there was no cyanosis or cherry red coloration. Examination of the head, eyes, ears, nose and throat showed pronounced conjunctival injection, soot in the mouth and nose, and erythematous oral and nasal mucous membranes. There was no stridor. Auscultation of the lungs disclosed occasional expiratory wheezes. The remainder of the physical examination showed no abnormalities.

Results of laboratory tests were as follows: hemoglobin 15.6 grams per dl, hematocrit 46.2 percent and leukocyte count 12,600 per cu mm. The serum sodium level was 138, potassium 4.6, chloride 100 and bicarbonate 22 mEq per liter; blood urea nitrogen was 14 and creatinine 1.1 mg per dl. Results of the SMA-12 analysis were within normal limits. A 12-lead electrocardiogram showed sinus tachycardia at a rate of 120 beats per minute. There were nonspecific ST segment and T wave abnormalities in all leads. A roentgenogram of the chest showed no abnormalities. Arterial blood gas measurements obtained while the patient was breathing oxygen through a nonrebreathing mask were pH 7.33, partial pressure of carbon dioxide 30 mm of mercury, partial pressure of oxygen (Po_2) 378 mm of mercury, calculated oxyhemoglobin saturation 99 percent and measured carboxyhemoglobin (COHb) saturation 45 percent. Sputum Gram stain showed 2+ polymorphonuclear leukocytes and carbon debris.

During the next ten hours the patient's dyspnea,

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†Diana Lewis Coleman, MD, Chief Resident in Medicine.

ABBREVIATIONS USED IN TEXT

Po_2 = partial pressure of oxygen
COHb = carboxyhemoglobin

hoarseness and wheezing worsened. Transnasal fiberoptic bronchoscopy showed substantial hypopharyngeal and laryngeal edema, and a nasotracheal tube was placed. Aminophylline was given intravenously and terbutaline subcutaneously, and the patient's wheezing lessened moderately. Oxygen therapy was continued and four hours after admission the COHb saturation was below 10 percent.

By the third hospital day, the laryngeal edema was decreased; however, suctioning yielded not only tenacious sputum but apparent bronchial casts as well. A temperature developed to 39.5°C (103.1°F). Arterial blood gas measurements showed increasing hypoxia, and a roentgenogram of the chest showed partial collapse of the right middle and right lower lobes, with pulmonary infiltrates. At bronchoscopy, plugs of mucus and debris nearly occluding the right middle and right lower segmental bronchi were seen. Sputum Gram stain showed 4+ polymorphonuclear leukocytes and both Gram-positive and Gram-negative organisms. The patient was treated with intravenously given penicillin and tobramycin. Sputum culture showed mixed oronasal flora and tobramycin administration was discontinued. The right middle and right lower lobes reexpanded fully and the patient's temperature returned to normal. By the eighth hospital day the patient's tracheal secretions were diminished considerably, and he was extubated.

At the time of discharge on day 14 the patient had no respiratory complaints. Findings of the physical examination and roentgenogram of the chest were normal as were arterial blood gas measurements.

Introduction

Fires causing large numbers of deaths have been recorded throughout this century in the United States. In 1903 a total of 602 people died in the Iroquois Theatre fire in Chicago. In 1930 a fire at an Ohio penitentiary killed 320, and 165 patrons died in Southgate, Kentucky, in 1977, when the Beverly Hills Supper Club burned. In November 1980 the fire at the MGM Grand Hotel in Las Vegas resulted in 84 deaths. Spectacular fires such as these understandably receive a great deal of attention by the press: a large number of people are at risk and major structures are threatened. However, the National Fire Protection Association (NFPA) estimates that hotel and motel fires accounted for only 0.4 percent of the 2,845,000 fires nationwide in 1979, whereas fires in other residential dwellings accounted for 25 percent of the total.[1] Approximately 140 civilians died and 1,225 were injured in the 11,500 hotel and motel fires in 1979. In contrast, 72 percent of the 7,780 total civilian deaths and 61 percent of the 31,325 total civilian injuries in the United States in 1979 resulted from the 710,000 residential fires that occurred that year. It is estimated that 55 percent to 80 percent of deaths due to fires result from smoke inhalation.[2]

Most of the morbidity and mortality resulting from the inhalation of smoke is a result of either systemic toxicity or complications from local respiratory tract injury. This paper will review the history and pathogenesis of smoke inhalation injury, the systemic illness resulting from inhalation of toxic gases, and the local effects from such inhalation on the respiratory system. Specific attention will be focused on carbon monoxide intoxication, the diagnosis of local injury to the respiratory system, the problem of upper airway obstruction, and the initial evaluation and management of patients with smoke inhalation injury.

Historical Background

The lethal qualities of smoke were appreciated as early as the first century AD, when Pliny the Elder recorded that prisoners were executed by placing them in cages suspended over green wood fires.[3] Medical attention was focused on the clinical significance of smoke inhalation and subsequent respiratory tract injury in 1942, when 489 persons died in the Cocoanut Grove Nightclub fire in Boston.[4,5] Of the 181 survivors who required hospital care, 170 were admitted to either the Massachusetts General Hospital (MGH) or Boston City Hospital.[4,5] Of the 39 people admitted to MGH, injuries to the respiratory tract developed in 36, and 7 of the victims died. In 97 of the 131 patients at Boston City Hospital, involvement of the respiratory tract developed, and 39 died. From these experiences it became apparent that smoke inhalation and subsequent injury to the respiratory tract were important causes of morbidity and death.

More recently, at the MGM Grand Hotel fire

in Las Vegas, more than 5,000 people were at risk of smoke inhalation or thermal injury. The NFPA estimated that at least 679 people were injured.[6] Within a few hours, more than 600 of the injured people received care at several hospitals; of these, more than 300 required hospital admission. Of the 84 deaths, 79 were a result of smoke inhalation. Most of the victims were found on the 20th through 25th floors of the hotel, far above the fire, which was confined to the first floor. They were often found clustered in elevator lobbies and in enclosed stairwells, two areas that filled with dense smoke during the fire.

Pathogenesis of Inhalation Injury

Smoke is a suspension of small particles in hot air and gases. The composition varies with the materials that undergo thermal degradation and combustion, the temperature of the process and the concentration of oxygen available.[7] The injury produced depends on the composition of the smoke and the duration of exposure.[8]

Smoke inhalation causes injury by thermal, chemical and hypoxemic mechanisms and results in systemic injury as well as damage to the upper and lower respiratory systems. Injury to the upper respiratory system is caused by both thermal and chemical processes. Injury to the lower respiratory system is usually due to chemical mechanisms. Systemic illness results from both chemical and hypoxemic processes.

Thermal Injury

In a series of experiments in 1944, the respiratory tracts of dogs were exposed to oven-heated air, flame and combustion products from a blast burner, and steam.[9] To prevent the animals from dying from obstructive asphyxia due to pharyngeal and laryngeal edema, the hot gases and combustion products were delivered through an insulated transoral cannula passed through the larynx directly to the trachea. The temperature of the inhaled mixtures was monitored by thermocouples located at the laryngeal end of the cannula and at the carina. The temperature of the heated air and blast flame mixtures ranged from 250° to 550°C at the laryngeal end of the cannula, and cooled to less than 100°C by the time the carina was reached. The temperature of the inhaled steam fell less dramatically from 100°C as it traversed the same path. Pathological examination of the tracheobronchial tree and pulmonary parenchyma showed tracheitis but no significant lung injury except when steam was used. This suggested that thermal injury alone played little role in respiratory tract injury below the larynx unless an agent with a high specific heat, such as steam, was involved.

TABLE 1.—*Common Toxic Products of Combustion**

Substance	*Toxic Products of Combustion*
Polyvinyl chloride	Hydrogen chloride, phosgene, chlorine
Wood, cotton, paper	Acrolein, acetaldehyde, formaldehyde, acetic acid, formic acid
Petroleum products	Acrolein, acetic acid, formic acid
Nitrocellulose film	Oxides of nitrogen, acetic acid, formic acid
Polyurethane	Isocyanate, hydrogen cyanide
Melamine resins	Ammonia, hydrogen cyanide

*Adapted from Fine et al.[10]

Chemical Injury

Subsequent experiments have confirmed the impression that thermal injury per se does not commonly cause injury to the lower respiratory tract, but that most of the damage is produced by toxic products of combustion. Thermal degradation and combustion of both man-made and natural materials in the environment result in the generation of numerous toxic chemicals.

Polyvinyl chloride is a synthetic compound commonly used in modern building furnishings and fixtures. It does not ignite until it reaches 475°C; however, from 225° to 475°C it loses 60 percent of its weight by thermal degradation. More than 75 known toxic products are formed in the process, including hydrogen chloride, phosgene and chlorine.[7] Combustion of other common materials results in the generation of numerous organic acids, aldehydes and other noxious gases, including oxides of sulfur and nitrogen (Table 1).[10]

Aldehydes, especially acrolein, cause irritation of the exposed mucous membranes, pulmonary edema and death.[8] Irritant gases such as ammonia and sulfur dioxide combine with water present in the mouth and tracheobronchial tree to form damaging alkalies and acids.[11] Soot aerosols absorb toxic gases such as hydrogen chloride and transport them to alveolar areas where they cause further damage.[12]

Mucosal edema, bronchorrhea, and sloughed mucosa caused by chemical injury increase airway resistance and cause obstruction to airways. Inhaled soot particles, in addition, cause broncho-

constriction, possibly by stimulation of irritant receptors in the airways.[13]

Chemical injury resulting from smoke inhalation depresses pulmonary defense mechanisms, which are further compromised by any associated cutaneous burns.[14-19] Bacterial pneumonia is, therefore, a common complication of inhalation injury.[20-25]

Hypoxemic Injury

Severe hypoxemia results most often from either asphyxia or carbon monoxide poisoning. Fire in a closed area progressively consumes the available oxygen, and various products of combustion dilute the concentration of the remaining oxygen, diminishing its partial pressure. This subsequently leads to hypoxia. Carbon monoxide intoxication is one of the most frequent immediate causes of death from smoke inhalation.[26]

Systemic and Local Respiratory System Effects

Illness resulting from smoke inhalation can be divided into two major processes: the systemic effects of toxic gases such as carbon monoxide that are absorbed from the respiratory tract and the direct local effects of the inhaled substances on the respiratory system.

Systemic Injury

Carbon Monoxide

Carbon monoxide, a ubiquitous product of incomplete combustion, causes death as a result of its systemic effects. In autopsy studies conducted in fire victims in Maryland and New York City, carbon monoxide caused or contributed to 80 percent of the fatalities that occurred within 12 hours of injury.[26,27] This colorless, odorless gas was cited as the sole factor responsible for failure to escape from a fire nearly 30 percent of the time, and, in combination with alcohol, it was cited an additional 34 percent of the time.[26]

Carbon monoxide produces its toxic effect by three mechanisms: It decreases oxygen transport by hemoglobin; it decreases oxygen unloading at tissues, and it impairs the use of oxygen by tissues. Because of the increased affinity of carbon monoxide for hemoglobin, the amount of hemoglobin available to bind oxygen is decreased and the oxygen-carrying capacity of the blood is reduced (Figure 1).[28] At a COHb saturation of 50 percent, the oxygen content of arterial blood at a partial pressure of oxygen (Po_2) of 100 mm of mercury is approximately 50 percent of normal. This is similar to that seen in an otherwise normal person whose hemoglobin concentration has been reduced by 50 percent. However, despite the similar oxygen contents, the patient with carbon monoxide

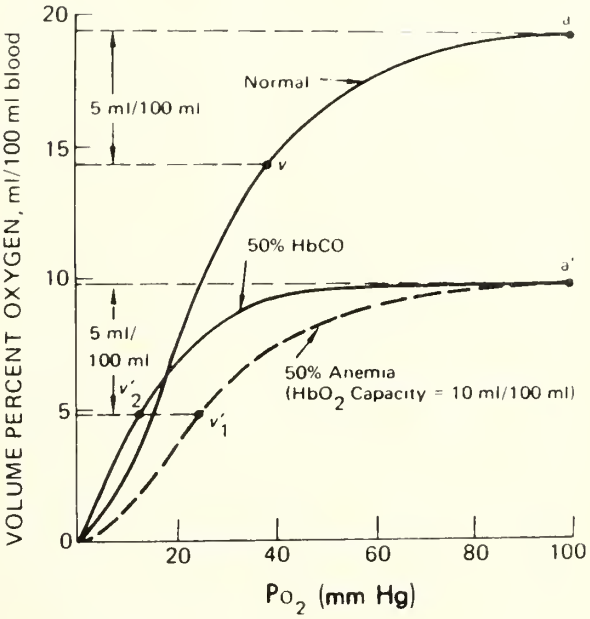

Figure 1.—Arterial blood oxygen content plotted against partial pressure of oxygen (Po_2) in a normal person, a person with 50 percent carboxyhemoglobin (COHb) and a person with anemia and a 50 percent reduction in hemoglobin concentration (HbCO). (Reproduced with permission from National Academy of Sciences.[28])

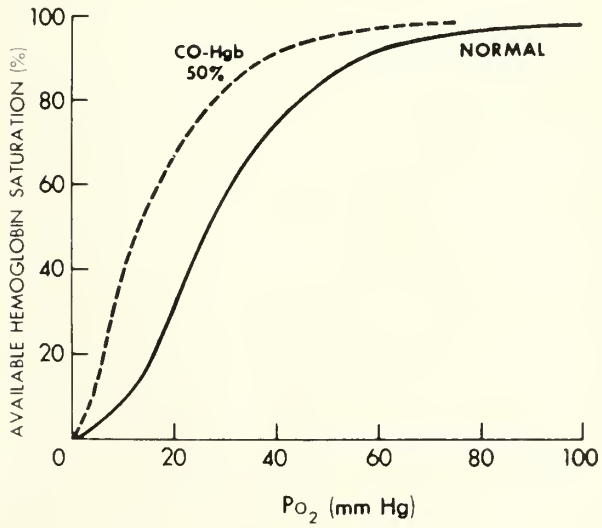

Figure 2.—Oxyhemoglobin equilibrium curve in a normal person and a person with 50 percent carboxyhemoglobin (CO-Hgb) (Po_2 = partial pressure of oxygen). (Reproduced with permission from Hinshaw & Murray.[29])

intoxication has less capacity for oxygen unloading at the tissues. This occurs because in the presence of COHb, the oxyhemoglobin dissociation curve is shifted to the left (Figure 2).[29] Therefore, for any given partial pressure of oxygen, more of the available hemoglobin remains saturated and less oxygen is available to the tissues. In addition, carbon monoxide may be directly toxic at the cellular level by its action on the cytochrome enzyme systems.[30]

The affinity of carbon monoxide for hemoglobin is approximately 200 times greater than oxygen's affinity for hemoglobin.[31,32] Therefore, even brief exposure to carbon monoxide can result in a significant COHb saturation. Endogenous production of carbon monoxide during metabolism of hemoglobin or other tetrapyrroles usually results in COHb saturation of less than 0.7 percent.[32] Mean COHb saturation in smokers of one pack of cigarettes a day has been reported at 1.9 percent and in smokers of two packs a day at 3 percent.[32] Smoke at fire scenes can contain carbon monoxide in concentrations that vary from 0.1 percent to 10 percent (1,000 to 100,000 ppm).[33] It has been calculated that a 30-second exposure to 1 percent carbon monoxide during heavy exertion such as might be involved in fighting or escaping from a fire (30 liters per minute alveolar ventilation) would result in a COHb saturation of 7.5 percent, and a two-minute exposure to the same concentration of carbon monoxide would result in a saturation of 30 percent.[33] A two-minute exposure to 2 percent carbon monoxide under the same conditions would produce a lethal COHb saturation of 60 percent (Table 2).

Signs and symptoms of carbon monoxide poisoning vary with the amount of COHb present (Table 3) and offer no pathognomonic clues for diagnosis.[34] Findings on examination of the skin may occasionally aid in the diagnosis. The classic cherry red skin color associated with the presence of COHb was observed in only 14 of 105 patients in one clinical series.[35] Cyanosis was a much more common finding, occurring in 43 of the 105 patients. Irregularly bordered erythematous skin patches, vesicles and bullae have also been noted.[36]

Carbon monoxide intoxication should always be suspected in persons found in fires. The diagnosis can only be inferred from routine arterial blood gas measurements. The measured oxygen content is always diminished; however, this determination is not routinely available. The Po_2 reading is usually normal, even in the patient with significant carbon monoxide intoxication. Therefore, the calculated oxyhemoglobin saturation is also normal. When present, an associated acidemia and elevated anion gap further raise the suspicion of carbon monoxide intoxication.[37] The definitive diagnosis relies on the measurement of blood COHb saturation. Because the COHb saturation begins to decrease as soon as the victim is removed from the carbon monoxide-containing environment and decreases more quickly if oxygen therapy is instituted, a normal COHb saturation in the emergency room does not exclude significant prior carbon monoxide exposure.

The half-life of COHb in a person breathing room air is approximately 250 minutes, but this declines to 40 minutes when 100 percent oxygen is breathed.[32] For this reason, fire victims should receive continuous supplemental high-flow oxygen therapy from the time they are removed from the fire until their COHb saturation is documented to be normal. Patients with severe carbon monoxide intoxication may require intubation and mechanical ventilation to allow delivery of 100 percent

TABLE 2.—*Increase in Blood Carboxyhemoglobin (COHb) Level During Heavy Exertion**†

Carbon Monoxide Concentration		*Increase in COHb Saturation After Brief Carbon Monoxide Exposure (%)*			
(ppm)	*(%)*	*10 sec*	*30 sec*	*60 sec*	*120 sec*
1,000	(0.1)	0.2	0.6	1.3	2.5
10,000	(1.0)	2.5	7.5	15.0	30.0
20,000	(2.0)	5.0	15.0	30.0	60.0
50,000	(2.0)	12.5	38.0	75.0	..
100,000	(10.0)	25.0	75.0	..	..

*"Heavy exertion" = Labor demanding an alveolar ventilation rate of 30 liters/minute.
†Adapted and reproduced with permission from Stewart et al.[33]

TABLE 3.—*Signs and Symptoms at Various Concentrations of Carboxyhemoglobin (COHb)**

Concentration of COHb (%)	*Signs and Symptoms*
0-10	None in previously healthy patients
10-20	Tightness across the forehead, mild headache
20-30	Throbbing headache
30-40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting and collapse
40-50	Same as above, with greater possibility of collapse, syncope, and increased respiratory and pulse rates
50-60	Syncope, increased respiratory and pulse rates, coma, convulsions, and Cheyne-Stokes respirations
60-70	Coma, convulsions, cardiorespiratory compromise, death
>70	Death

*Modified from Schulte.[34]

oxygen and effective elimination of carbon monoxide. Hyperbaric oxygen and controlled hypothermia have also been advocated but are seldom available in time to be beneficial.[38]

Other Agents

Carbon monoxide intoxication may occur alone or be compounded by inhalation of other systemically active substances. Both carbon monoxide and cyanide were found in the blood of 39 of 53 persons who died in house fires.[39] In the remaining 14, only carbon monoxide was detected. In studies using rats, a reactive phosphate fire retardant has been shown to cause systemic toxicity that manifests as abnormal behavior, seizures and death, if the treated material continues to burn.[40]

Local Respiratory System Effects

Smoke inhalation victims are at risk of exposure to numerous other agents that cause not only systemic toxicity but also local damage to the respiratory system. Injury may occur at (1) the level of the upper airways, including the mouth, pharynx and larynx, (2) the lower airways, including the trachea, bronchi and bronchioles and (3) the pulmonary parenchyma. Local injury is a major cause of morbidity and mortality in burn patients. In one study 29 of 66 burn patients with local respiratory tract injury died as a result of respiratory complications.[21] In another study 94 of 197 patients died, and 69 of the deaths resulted from respiratory tract involvement.[22] The overall mortality of those burn patients with inhalational injury is two to four times that of patients without such injury.[20,41-44]

Diagnosis

There are no uniform criteria for making the diagnosis of local respiratory system damage or direct inhalational injury. Numerous clinical criteria have been described. The classic triad required for diagnosis of direct inhalational injury is the presence of thermal burns involving the face, particularly the mouth and nose, singed nasal vibrissae and a history of the burn injury being sustained in a closed space.[23] A combination of the above criteria, plus a history of inhalation of large amounts of smoke, the presence of carbonaceous sputum and clinical symptoms of wheezing, hoarseness or dyspnea have also been used.[21] Still other clinicians have required only that the patients have been exposed to the smoke of a fire and have sustained no more than minor cutaneous burns.[45] Patients with direct inhalation injury, as reported in the literature, vary considerably in the extent of the body surface area that has been burned, but most have sustained cutaneous burns.

The incidence of direct injury diagnosed by these various clinical criteria varies from 2.9 percent to 15.1 percent of all burn patients.[21,22,24,41] Clinical findings mirror the diagnostic criteria and include facial and oropharyngeal burns, cyanosis, dyspnea, tachypnea, cough, hoarseness, wheezes, rales, rhonchi and the presence of carbonaceous sputum.[21,23] In these clinically diagnosed patients, positive findings on auscultation of the chest at the time of admission[23] or development of cough, dyspnea, cyanosis, rales, rhonchi or wheezes within the first few hours after injury[24]—before significant fluid resuscitation occurred—were identified as poor prognostic indicators.

In the past decade much effort has been made to improve the accuracy of the early diagnosis of direct inhalation injury in burn patients. Radioactive xenon lung scanning and bronchoscopy have been studied the most. Inhalation injury is diagnosed by xenon lung scan if a prolonged length of time is taken to clear the xenon from the lungs or if segmental retention of the isotope occurs after intravenous administration.[43,44] Such abnormalities on scanning are associated with a history of injury in a closed space, findings of hoarseness and wheezing on physical examination, the presence of carbonaceous sputum, subsequent development of abnormalities found on roentgenograms of the chest and increased mortality. Poor correlation is seen with the presence of facial or intraoral burns. False-positive findings of xenon lung scans may occur in patients with preexisting bronchitis, bronchiectasis, asthma or pneumonia.[43] Inhalation injury is diagnosed bronchoscopically when laryngeal or tracheobronchial erythema or edema, carbonaceous material or bronchorrhea is seen.[42,46] With more extensive injury, blisters, ulceration, hemorrhage or necrosis may be present.

The incidence of direct inhalation injury in burn patients varies from 30 percent to 60 percent when these two specialized diagnostic techniques are used.[20,42-44] However, diagnosis of direct inhalation injury by either of these two methods does not specifically predict the subsequent occurrence of pulmonary complications. While respiratory problems developed in less than 10 percent of burn patients with negative findings on bronchoscopy or xenon scans, in 25 percent to

50 percent of patients with positive findings, clinically significant pulmonary complications did not develop.[20,42-44]

Roentgenograms of the chest, arterial blood gas measurements, cytologic evaluation of sputum and pulmonary function tests have also been examined as a means of making an early diagnosis of direct inhalation injury. Findings on chest x-ray films at admission are usually normal.* Determination of arterial blood Po_2, obtained while the patient is breathing room air at the time of admission, may also be within normal limits.[42] A progressive increase in the alveolar-arterial oxygen gradient was useful in predicting subsequent pulmonary dysfunction in a retrospective review of the clinical course of 41 burn patients considered at risk of inhalation injury.[49] The alveolar-arterial oxygen gradient measured while breathing 100 percent oxygen at 12 to 24 hours after injury was greater in patients whose condition subsequently deteriorated, and it increased even further 48 to 72 hours after the injury. Cytologic evaluation of expectorated ciliated epithelial cells has been suggested in one preliminary report to be a noninvasive way to diagnose damage to the airways.[50] Pulmonary function studies carried out in small numbers of patients with acute smoke inhalation have shown increased work of breathing, increased airways resistance, decreased flow rates and decreased lung compliance.[48,51-53]

At present the diagnosis of local respiratory system injury from smoke inhalation is a clinical one despite the variable clinical diagnostic criteria. When present, the diagnosis is supported by abnormal arterial blood gas measurements, findings of chest roentgenograms or pulmonary function tests. The routine use of bronchoscopy for direct visualization of the lower airways or of xenon lung scans is not recommended. The one critical exception to the predominantly clinical evaluation of patients with direct inhalation injury is that the patency of the upper airway must be evaluated by direct observation.

Upper Airway Obstruction

Obstruction of the upper airway from extreme laryngeal edema is a potentially lethal complication of smoke inhalation that requires prompt diagnosis and aggressive management. In one study, 8 of 33 patients with direct inhalation injury required intubation for laryngeal edema and obstruction of the airway,[20] and 5 of 15 required intubation for either obstruction of the airway or progressive respiratory insufficiency in another.[42] Edema and obstruction of the upper airway usually develop within 24 hours of injury.[51] Early clinical signs include tachypnea, hoarseness and stridor; however, these signs do not distinguish patients who progress, often precipitously, to complete airways obstruction.[20,54]

Direct visualization of the larynx can be used to identify patients at risk of developing progressive obstruction of the upper airway. Wanner and Cutchavaree[54] used fiberoptic transnasal laryngoscopy to examine 12 of 15 patients with a history of smoke inhalation and respiratory signs and symptoms of hoarseness, cough, dyspnea, wheezing and rhonchi. Of these, 3 had severe laryngeal edema; in 2 of these 3, the condition progressed to require intubation for maintenance of an adequate airway. The remaining nine patients displayed lesser degrees of edema and inflammation and showed no evidence of progressive airway obstruction.

Early direct visualization of the larynx should be done in any patient with a history of smoke inhalation and respiratory signs and symptoms including dyspnea, cough, hoarseness, stridor, tachypnea, wheezing or rhonchi. Patients with severe edema should undergo intubation.[54,55] If the initial examination of the larynx does not suggest the need for intubation but the patient's condition deteriorates, repeat visualization of the larynx is indicated. The edema usually subsides within three to five days of injury, and unless further complications are present, extubation is then possible.[20,55,56]

Long-term Complications

The long-term complications of local respiratory system injury are not well characterized. In the Cocoanut Grove disaster, 27 survivors who sustained mild-to-severe involvement of the respiratory tract were asymptomatic, with normal findings on physical examination and roentgenograms of the chest nine months later.[4] Tracheal stenosis, bronchial stenosis, bronchiolitis obliterans, endobronchial polyposis and bronchiectasis have been occasionally reported.[21,57-60]

Management

Initial Evaluation

An approach to the initial evaluation of a patient with smoke inhalation is summarized in Table 4. Historical details of the inhalation ex-

*20-22, 24, 25, 42, 47, 48

posure allow the types and degree of injury to be anticipated. Preexisting cardiopulmonary or central nervous system illness will affect the patient's ability to tolerate the additional insult.

During the physical examination positive findings on auscultation of the chest or findings suggestive of obstruction of the upper airway should be sought as should evidence for cardiac or neurological dysfunction. Quantification of the extent of the burn and the presence of other injuries such as lacerations or fractures should also be noted.

Determination of COHb saturation should be carried out in every patient. The need for additional studies will be suggested by the history and clinical findings. The clinical diagnosis of local respiratory system injury is supported by associated abnormal arterial blood gas measurements and abnormal findings of chest roentgenograms and bedside pulmonary function tests. At the initial evaluation, the question of the patency of the patient's upper airway must be raised and the need for laryngoscopy considered.

TABLE 4.—*Initial Evaluation of a Smoke Inhalation Victim*

History: Ascertain
- What were the circumstances of injury—closed area?
- What material was burned?
- Was there steam exposure?
- What prior cardiopulmonary or CNS diseases are present?
- What respiratory, cardiac, CNS symptoms are present?

Physicial examination: Observe for
- Tachypnea
- Facial, oropharyngeal, nasal hair burns
- Hoarseness, stridor, wheezing, rales, rhonchi
- Abnormal cardiovascular or neurological findings
- Burn extent and other injuries

Laboratory: Obtain
- Sputum specimen for carbonaceous material
- Arterial blood gas measurements: P_{O_2}, P_{CO_2}, pH, COHb
- Roentgenogram of chest
- Electrocardiogram
- Bedside pulmonary function tests: FEV_1/FVC
- Laryngoscopy

CNS = central nervous system; COHb = carboxyhemoglobin saturation; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

TABLE 5.—*Treatment of Smoke Inhalation*

At the scene of the fire
- Maintenance of an adequate airway
- Delivery of supplemental oxygen therapy
- Provision of basic resuscitative measures

In the hospital
- Assessment of airway patency
  - Laryngoscopy
  - Intubation
- Maintenance of adequate pulmonary toilet
- Delivery of humidified supplemental oxygen therapy
- Use of bronchodilator therapy
- Preparation of sputum Gram stain
- Replacement of fluid losses

Treatment

The treatment of patients with inhalation injury is, for the most part, supportive and is outlined in Table 5. Specific variations reflect the toxicology of any inhaled substances that are identified. At the scene of the fire, maintenance of an adequate airway and administration of oxygen to treat presumed carbon monoxide intoxication are priorities along with other basic resuscitative measures.

Once at the hospital, assessment and treatment of the patient's injuries from smoke inhalation, thermal burns and other trauma continue. Severe laryngeal edema observed on direct visualization of the larynx is an indication for intubation. Attention should be focused on maintaining adequate pulmonary toilet and on delivery of humidified supplemental oxygen. Bronchodilator therapy is useful in treating the bronchospastic component of the airway obstruction. Because of the increased risk of pneumonia, daily sputum Gram stains should be done and findings correlated with the patient's clinical course. Prophylactic antibiotic therapy has no demonstrated role in patients with direct inhalation injury.[11,22,24]

The use of corticosteroids in the treatment of direct inhalation injury has been recommended by some, but the results of most studies do not support their use. In one controlled study of rats exposed to white pine smoke, methylprednisolone or dexamethasone improved survival.[3] However, dexamethasone had no effect on mortality or morbidity in a prospective randomized study of 30 humans.[61] Furthermore, a partially randomized study of 33 patients treated with methylprednisolone showed a threefold increase in the occurrence of pneumonia and bacteremia and a fourfold increase in mortality.[20] At a consensus development conference on supportive therapy in burn care in 1978, the recommendation was made that corticosteroid therapy should not be used in the treatment of direct inhalation injury.[62]

Judicious administration of fluids should be monitored by following blood pressure and urine output. Measurement of pulmonary capillary wedge pressure and cardiac output should be used

to guide fluid therapy in patients with hemodynamic compromise.[63,64]

After discharge, subsequent evaluation with measurement of arterial blood gases, pulmonary function studies and bronchoscopy should be guided by the patient's clinical status; these are not routinely recommended.

Admission Guidelines

Widely accepted guidelines are not available to aid clinicians in deciding which patient with smoke inhalation injury should be admitted to hospital. In Table 6, several findings are listed that, if present, should suggest the need for further observation in an inpatient setting. Patients whose initial assessment does not indicate the need for admission should be reassessed over the next 6 to 12 hours. Deterioration of clinical status or laboratory values is an indication for hospital admission.

TABLE 6.—*Guidelines for Admission of Patients With Smoke Inhalation Injury*

Presence of significant thermal or other injuries
Symptoms, signs or laboratory evidence of cardiac or CNS dysfunction
Physical examination findings of: tachypnea, hoarseness, stridor, wheezing, rales, rhonchi
COHb saturation >15% to 20% on arrival
Abnormal results of chest roentgenogram, arterial blood gas measurement, pulmonary function tests
Deterioration in clinical status, arterial blood gases, pulmonary function tests

CNS = central nervous system; COHb = carboxyhemoglobin

TABLE 7.—*Guidelines for Fire Safety in High-Rise Buildings**

Know the location of two exit stairs near your room.
Count the number of doors between you and the exit stair so that the exit can be found by feel in a smoky and dark hallway.
Never use the elevator in the event of a fire.
Know where the room key is and always take it with you when you leave the room so that you will not be locked out.
Report any fire you discover to the building personnel and to the fire department.
Avoid breathing the smoke.
Seal cracks around the door of your room and try to close any air ventilators in the room.
Feel the door before opening it. If it is hot, keep it closed.
Do not walk into smoke. Stoop down or crawl.

*Adapted from the pamphlet "If You Work . . . If You're Staying or Live in a High-Rise You Can Survive! But It's Up to You," available from the Community Relations Section, Fire Prevention Bureau, Los Angeles County Fire Department.

Prevention

It has been stated that an ounce of prevention is worth a pound of cure. The use of smoke detectors provides an early warning system that is lifesaving. Knowing in advance what to do if trapped in a burning building or smoked-filled area may mean the difference between survival and death. Table 7 summarizes warnings and guidelines issued by the Los Angeles County Fire Department in an effort to improve survival in fires in high-rise buildings.

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Important Advances in Clinical Medicine

Epitomes of Progress — Chest Diseases

The Scientific Board of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in chest diseases which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Immunization Against Lung Infections

PULMONARY INFECTIONS remain an important cause of morbidity and mortality in patients with chronic cardiac or pulmonary disease and certain other conditions. Immunization is available against influenza virus and pneumococci, two of the most common pulmonary pathogens.

Influenza vaccine, available since the 1940's, is made from representative strains of influenza A and B virus grown in embryonated eggs and then chemically inactivated. Recent advances in vaccine production include (1) enhanced yields of vaccine virus by genetic recombination, (2) purification of vaccine virus by zonal centrifugation, which reduces side effects, (3) development of a subvirion ("split-virus") vaccine that contains detergent-disrupted virions with lessened side effects and (4) development of a rational standardization procedure for the vaccine based on content of a specific virus protein, hemagglutinin, which is well correlated with antigenicity in humans.

Influenza vaccine is 70 percent to 80 percent effective in preventing influenza and is indicated annually (generally in the fall) for those with a high risk of serious complications from influenza. Patients with physiologically significant cardiac or pulmonary disease as well as those with azotemia, chronic anemia and certain other conditions should be immunized. The vaccine is also recommended for healthy persons 65 years and older. Split-virus vaccine should be used for children because it has a lower incidence of side effects than whole-virus vaccines in this age group. Influenza vaccine is a safe product; specifically, the increased incidence of Guillain-Barré syndrome following swine influenza immunization has not been seen with the present product, despite intensive monitoring.

Pneumococcal vaccine also was first used clinically in the 1940's but was withdrawn from the market when penicillin became widely available. The present pneumococcal vaccine is a mixture of purified polysaccharides from the 14 most common pneumococcal serotypes. In field trials it is about 80 percent effective in preventing pneumonia due to homologous types and about 50 percent to 60 percent effective in preventing pneumococcal pneumonia overall. Comparable efficacy was observed in preventing more serious infections in asplenic children. It is likely that the vaccine will be effective against pneumococcal infections in other sites as well, although this has not been

documented as yet. One retrospective epidemiologic study, however, failed to show efficacy in young children (aged 2 to 10) or high-risk adults, although the vaccine was protective in other patient groups.

Pneumococcal vaccine is indicated for immunization of patients at high risk of pneumococcal infection, including candidates for influenza vaccine, functionally asplenic patients (such as patients with sickling hemoglobinopathies) and selected other patients at high risk of pneumococcal infections (such as recurrent otitis media or nephrotic syndrome). Patients in closed communities (for example, nursing homes) are at increased risk of pneumococcal infection, and use of the vaccine should be considered in this setting as well. Unfortunately, this and other polysaccharide vaccines are relatively nonimmunogenic and ineffective in children younger than two years of age. The reimmunization interval has not been finally established but will probably be no more often than every five years. Toxicity has been mild and infrequent.

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Broome CV, Facklam RR, Fraser DW: Pneumococcal disease after pneumococcal vaccination: An alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 303:549-552, Sep 4, 1980

Small Cell Carcinomas of the Lung

APPROXIMATELY 8 percent to 15 percent of all types of primary lung cancer are of the small cell variety. They are characterized by aggressive clinical behavior and histological features that suggest their derivation from neuroectodermal tissue.

Fewer than 5 percent of these small cell tumors are detected at an asymptomatic stage; they typically grow very rapidly and metastasize early and widely—underlining the importance of establishing a histological diagnosis in patients suspected of having this disease. This can usually be achieved by means of sputum cytology, bronchoscopy, mediastinoscopy or aspiration needle biopsy.

Because of the tumor's rapid growth, results after resection are poor, and this type of malignancy is generally considered to be inoperable at any stage. However, relative success has been reported with nonsurgical therapy. Small cell types of cancer typically respond to combinations of chemotherapy given with or without radiation. Numerous therapy programs have shown good results, with survival of patients having been extended for several months and, in some cases, years. A "best" therapy has not yet been established.

Recently, interest has returned to surgical intervention as adjuvant therapy wherein the primary lesions are removed as part of a chemotherapy program. Because these are active and important areas of clinical investigation, patients should be treated in one of many centers where the results of various approaches can be evaluated.

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Aspiration Pneumonitis

THE ASPIRATION of stomach contents can lead to serious consequences in patients with altered states of consciousness or abnormalities of swallowing or in those undergoing anesthesia.

Substantial quantities of fluid aspirated into the lung can cause acute respiratory decompensation. If the fluid pH is greater than 2.5, is free of food particles and is isotonic, recovery is likely. If it has a pH of less than 2.5, is hypertonic and contains food particles or nonparticulate food substances, a progressive inflammatory reaction may develop. Acid aspirates produce the greatest anatomic and physiological harm.

The causative role of infection remains unclear. If necrotizing pneumonia, lung abscess or empyema develops, then a heavily infected inoculum was probably aspirated. In patients not in hospital, the organisms are usually anaerobes; whereas, facultative anaerobes (Gram-negative rods) and aerobes are predominant in patients in hospital. A delayed infection may develop in some patients and is probably due to contamination of the chemically damaged lung by artificial airways, suction and mechanical ventilatory apparatus. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are frequent isolates in these circumstances. There is no characteristic radiographic pattern in this disease. Severe hypoxemia is the predominant gas-exchange alteration.

In a surgical patient the preoperative administration of 400 to 600 mg of cimetidine has been

described as a useful tool to lower the risk of aspiration pneumonitis.

Endotracheal suctioning is an important initial therapeutic step. Because the aspirated material is rarely entirely removed, other therapeutic measures are also required. Bronchoscopy should be done on anyone who has aspirated particulate matter, especially if there is clinical or radiologic evidence of segmental loss in lung volume. Routine bronchial lavage with neutral or alkaline solutions is not effective, and the use of corticosteroids remains controversial. Although prophylactic antibiotics have been advocated, their effectiveness is doubtful because their use has demonstrated no proved benefit on ultimate outcome. A more logical approach is to closely monitor the patient for clinical and bacteriologic evidence of infection using uncontaminated specimens of tracheal aspirates.

When the patient's hypoxemia can no longer be corrected without using toxic levels of oxygen, positive end-expiratory pressure should be instituted. The actual level of pressure required will vary with each patient, but levels as high as 30 cm of water occasionally have been necessary. Barotrauma, such as pneumothorax, and impaired cardiovascular function should be anticipated and, when present, appropriately treated.

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Long-term Use of Oxygen Therapy

OUTPATIENT OXYGEN THERAPY (OPOT) has improved the survival rate and neuropsychological function, as well as lowering pulmonary hypertension and erythrocytosis, in selected patients with hypoxemic chronic obstructive pulmonary disease (COPD). Continuous (21 to 24 hours per day) OPOT reduces mortality substantially as compared with the 12-hour (per day) regimen. Treatment programs providing less than 12 hours a day of OPOT have no proven benefit except for relieving subjective symptoms or improving exercise tolerance while the patient is breathing oxygen.

In most patients with COPD, improvement of hypoxemia will occur once pulmonary or cardiopulmonary exacerbations are properly treated. Short-term oxygen therapy is used during exacerbations until resting arterial oxygen exceeds 55 to 60 mm of mercury. When the patient's condition has been stable for a month following discharge from hospital, a decision regarding long-term OPOT should be made. Cor pulmonale, erythrocytosis, mental changes and sleep disorders are clues to possible persistent hypoxemia and a need for OPOT; however, these may be lacking or unrecognized.

Obtaining arterial blood gas measurements on several occasions during a one-month stability period will aid the prescriber in determining whether long-term OPOT is needed.

In selected COPD patients, OPOT will improve exercise tolerance. Most patients with COPD have exercise limitations and breathlessness unrelated to hypoxemia. There are no conclusive studies as to whether chronically hypoxemic and stable patients with diseases other than COPD benefit in a similar manner or degree from long-term OPOT.

Proper patient selection is important because OPOT is expensive ($200 to $400 per month) and easily mistaken as a panacea. Stable outpatients with an arterial oxygen pressure (Pa_{O_2}) of 55 mm of mercury or less are considered candidates for OPOT. A patient with a Pa_{O_2} of between 55 and 60 mm of mercury may be treated when cor pulmonale or erythrocytosis is present. The adequacy of the prescribed OPOT dose should be established every three to four months. Oxygen supplementation should provide a Pa_{O_2} of 60 to 80 mm of mercury. Careful patient education, often underemphasized, is essential.

OPOT is usually administered during sleep because there is a greater likelihood of severe prolonged desaturation during this time. A small increment to the daytime flow rates often is necessary to maintain adequate sleep oxygenation.

Cost, convenience and familiarity are the determining factors for choice of OPOT equipment. When properly instructed and monitored, OPOT has proved to be safe, with rare and usually minor problems. The new oxygen concentrator systems have the advantage of necessitating fewer home visits by the supplier. A portable back-up system should augment the concentrator because the latter is not mobile and is subject to electrical power failures.

Long-term OPOT, although beneficial for selected hypoxemic patients, is only one component of a

comprehensive outpatient care program to minimize the incidence of mortality, morbidity and admittance to hospital. Proper selection and education of patients as well as follow-up analyses will help to avoid financial waste, unrealistic expectations and poorly coordinated treatment regimens.

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Computed Tomography in Lung Disease

COMPUTED TOMOGRAPHIC (CT) scanning in patients with lung disease has proved useful in (1) detection and evaluation of solitary pulmonary nodules, (2) detection of pulmonary metastasis, (3) diagnosis and evaluation of vascular lung lesions, (4) distinguishing between pulmonary parenchymal and pleural processes, (5) the detection and evaluation of diffuse pulmonary disease and (6) carrying out percutaneous needle aspiration biopsy.

In general, CT is more sensitive than are plain radiographs or conventional tomograms in the detection of single or multiple pulmonary nodules. For this reason, CT is largely replacing conventional tomographic studies for the detection of nodular disease. In patients with a solitary nodule visible on plain radiographs, CT can be used to search for other nodules or associated mediastinal adenopathy; CT is also more sensitive in detecting mediastinal lesions. CT densitometry of solitary nodules may be of some value in distinguishing benign and malignant lesions, the presumption being that benign lesions often contain calcium invisible on plain radiographs but detectable by CT. In one study, excellent results were obtained by measuring the CT number of lung nodules detected. However, these results have been difficult to duplicate, and CT nodule densitometry, at this time, must be considered experimental or of limited clinical value.

Because of its enhanced sensitivity and ability to view the mediastinum, CT should replace other radiographic procedures in the detection of pulmonary metastasis in most cases.

Dynamic CT scanning following a bolus injection of contrast material can be used to diagnose and evaluate pulmonary vascular lesions, such as arteriovenous fistula, pulmonary vein varix and sequestration. However, vascular tumors (bronchial adenoma) sometimes may produce false-positive results. In some cases, CT may replace arteriography.

Because of its cross-sectional format, CT is ideally suited to the distinction of pulmonary parenchymal disease and pleural disease when plain chest radiographs are equivocal. However, although CT has been reported helpful in differentiating empyema and lung abscess, this distinction can be difficult.

CT is extremely sensitive in detecting subtle differences in density and can show pulmonary fibrosis in patients with various lung diseases (such as sarcoidosis or asbestosis) when plain chest radiographs show no abnormalities. Also, CT shows areas of decreased density (such as bullae or emphysema) better than other radiographic techniques.

Lastly, in patients with pulmonary lesions requiring percutaneous biopsy, CT can be extremely useful in needle placement and precise localization of the needle tip. By using CT, lesions in the lung that are close to vascular structures can be safely approached.

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Diagnosis and Management of Goodpasture's Syndrome

GOODPASTURE'S SYNDROME involves a triad of glomerulonephritis, pulmonary hemorrhage and antiglomerular basement membrane antibody (anti-GBM) production. The cause of this disorder is unknown, although some patients have a history of recent viral illness or exposure to volatile hydrocarbons. It is an uncommon but serious disorder in which a rapidly progressive, crescentic glomerulonephritis develops, which leads to uremia. Pulmonary hemorrhage in the syndrome may be life-threatening, and evidence of its presence—that is, hemoptysis, infiltrates noted on x-ray films, reduced arterial oxygen tension, hemosiderin-laden macrophages and iron deficiency anemia—is

found in 50 percent to 75 percent of cases. Increased pulmonary carbon monoxide uptake is present in nearly all patients, and is a sensitive test of pulmonary hemorrhage.

Goodpasture's syndrome must be distinguished from other causes of glomerulonephritis and pulmonary hemorrhage such as systemic lupus erythematosus or necrotizing vasculitis where tissue injury is mediated by immune complexes. Also, in patients with established renal failure, pulmonary hemorrhage caused by pneumonia, pulmonary emboli or a bleeding diathesis can develop. Accurate diagnosis depends on detection of circulating anti-GBM antibody, present in more than 90 percent of patients, by indirect immunofluorescence or radioimmunoassay and by kidney or lung biopsy and the demonstration of *linear* IgG deposits along the basement membrane. Absence of such *linear* IgG deposits in a kidney biopsy excludes the diagnosis of Goodpasture's syndrome. However, the reliability of lung biopsy findings has not been established and a negative study may not be definitive. Circulating anti-GBM antibody levels do not correlate with severity of clinical manifestations. If properly done, examination of serum for anti-GBM antibodies rarely gives false-positive results. While *linear* IgG deposits along the GBM in the kidney also occurs in diabetes and occasionally in other conditions, the use of proper immunofluorescence controls can usually aid in distinguishing between these conditions.

High doses (10 to 20 mg per kg of body weight) of methylprednisolone ("pulse therapy") and intensive plasma exchange (plasmapheresis) appear to represent important new treatments for pulmonary hemorrhage in Goodpasture's syndrome and have largely replaced the questionable practice of bilateral nephrectomy for life-threatening disease. Plasmapheresis will quickly reduce the level of circulating anti-GBM antibody. For severe pulmonary hemorrhage unresponsive to "pulse therapy," daily plasma exchanges (3 to 4 liters) may be done using semiautomated, gravity-sedimentation (centrifugation) techniques for separating formed elements from plasma. The removed plasma may be replaced with plasma protein fractions or fresh frozen plasma. Plasma exchange is combined with oral administration of prednisone (1 mg per kg of body weight per day), cyclophosphamide (2 mg per kg of body weight per day) and, in patients younger than 50, azathioprine (1 to 2 mg per kg of body weight per day). Daily or every-other-day exchanges are continued until there is clear evidence of clinical and laboratory improvement, and the drugs are administered for two to six months or longer. In most patients cessation of pulmonary hemorrhage occurs within 24 to 72 hours of initiating plasma exchange treatment. If renal failure is not advanced (serum creatinine <6 mg per dl), renal function often stabilizes or improves. Infection must be scrupulously avoided because it may exacerbate the pulmonary hemorrhage and renal failure.

Surprisingly, anti-GBM antibody levels do not parallel the improvement and should not be used as a sole guide for treatment. Plasmapheresis is not a substitute for hemodialysis and both procedures may be carried out concurrently. Patients with advanced renal failure (serum creatinine levels greater than 10 mg per dl) and severe glomerular and tubulointerstitial lesions may not experience any improvement in renal function and may require maintenance hemodialysis. Renal transplantation is not contraindicated but should be deferred until anti-GBM antibody levels have decreased to low or undetectable levels. Recurrence of disease in the allograft may occur but usually is not severe enough to result in graft failure.

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Increased-Permeability Edema of the Lung

OF THE TWO CHIEF TYPES of acute pulmonary edema—that due to increased pressure and that due to increased alveolar capillary barrier permeability (formerly called noncardiogenic edema)—the latter has been the focus of much clinical and experimental attention for three reasons: its rapid course, its development in otherwise healthy persons and an emerging understanding of its pathophysiology.

The chief clinical characteristics of increased-permeability edema are as follows: a specific inciting event, rapid time course, high edema fluid to plasma protein concentration ratio and pulmonary artery wedge pressure usually within the broad range of normal. Wedge pressure elevation does

not preclude increased-permeability edema of the lung. Therefore, measurement of the wedge pressure may be helpful as a guide to treatment, but the absolute value by itself is not diagnostic. Some of the frequent causes of increased-permeability edema include traumatic shock, Gram-negative sepsis, microembolism, drug overdoses or idiosyncrasies, gastric acid aspiration, central nervous system dysfunction and high altitude.

Although this form of edema has diverse causes, much interest has focused on the role of circulating blood elements. Neutrophils in particular, but also platelets and fibrin, appear to be directly involved in the development of some types of increased-permeability edema.

Usually, the initiating event is of brief duration and is self-limited. Severe edema can occur with relatively modest injury to the lung's microcirculation; however, because the recuperative properties of the microvascular endothelium are great, supportive therapy often leads to quick recovery.

In patients at high risk, such as those with extensive body burns or those who have sustained serious trauma, pharmacologic doses of corticosteroids (30 mg per kg of body weight) appear to attenuate the subsequent injury process; however, there is no evidence that corticosteroids are useful after the edema process has developed.

There is no specific treatment for the developed injury, although it is obvious that the inciting process should be controlled or eliminated. Supportive therapy, in addition to adequate systemic oxygenation, involves manipulating the hydrostatic and colloid osmotic pressures that affect lung fluid balance. Positive end-expiratory pressure (PEEP) breathing with or without oxygen may be useful to expand the air spaces and increase arterial oxygenation, but it has little effect on lung fluid balance. Some investigators believe that high pressure PEEP may increase the edema. While protein or other colloid-containing fluids may be of value in hypoproteinemic patients when the microvascular barrier integrity is normal, they are not of value in treating increased-permeability edema during the acute phase. However, a patient who is hypoproteinemic may be helped by colloids, which act to extract fluid from noninjured tissues (including those portions of the lung that are not injured), thus maintaining circulating blood volume and cardiac output.

The most important point to remember in managing lung fluid balance is that the pressure that drives ventricular filling (cardiac output) is the same pressure that causes fluid to filter into the lung. The current trend is for less volume loading, direct measurement and control of cardiac output and afterload reduction to reduce ventricular filling pressure and the pressure in the pulmonary microcirculation.

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Respiratory Disturbances in Sleep

TWO TYPES of respiratory disturbances that occur in sleep are multiple episodes of apnea (cessation of ventilation for 10 seconds or more) and disordered breathing (such as apnea, decreased tidal volume or an irregular breathing rate) in patients with chronic obstructive pulmonary disease (COPD). Multiple apneas can lead to the sleep-apnea syndrome; disordered breathing can contribute to the morbidity and mortality of patients with COPD.

In patients with normal pulmonary function who have both excessive daytime sleepiness (EDS) and loud snoring during sleep, the sleep-apnea syndrome is a likely cause. Most such patients are male and obese; many have impotence, mild systemic hypertension and a change in personality, and a few have chronic cor pulmonale.

The sleep-apnea syndrome is confirmed by demonstrating 30 or more nocturnal episodes of apnea, some of which are repetitive during non-rapid-eye-movement sleep. This is best accomplished in a laboratory that is equipped to monitor and record at least eight hours of sleep, respiratory data and an electrocardiogram. The diagnosis is usually obvious, with hundreds of apneic episodes being recorded. Most apneas lead to a decrease in arterial oxygen saturation of 3 percent or more (usually much more). Further, sinus bradycardia almost always occurs, and asystole occasionally occurs during the apneas.

Apneic episodes can be classified into three types. Central apnea results from a disturbance of the central nervous system, which leads to cessation of respiratory muscular contraction. In peripheral (or obstructive) apnea, respiratory muscular efforts continue, but ventilation is prevented because the upper airway is completely occluded by flaccid soft tissues of the pharynx. In-

complete occlusion also occurs, which leads to snoring. Mixed apnea is central apnea followed by peripheral apnea in the same continuous apneic episode. Most patients with the sleep-apnea syndrome have peripheral and mixed apneas.

Treatment of the sleep-apnea syndrome can include loss of weight, oral administration of medroxyprogesterone acetate (10 to 20 mg three times a day), or both. These modalities are most effective in patients with cardiorespiratory failure and obesity (that is, the Pickwickian syndrome). Some patients with sleep apnea have oral or nasopharyngeal deformities (for example, enlarged adenoids). Correction of these deformities may relieve peripheral and mixed apneas.

Tracheostomy can be done to bypass the nocturnal occlusion of the upper airway, but this treatment should be reserved for patients with peripheral and mixed apneas who have disabling EDS, life-threatening arterial oxygen desaturation, or life-threatening sinus bradycardia or asystole. A tracheostomy can be done initially as an urgent form of treatment, but it is usually done after other therapy fails. When the tracheostomy tube is left open at night and closed during the day, remission of clinical findings is usually dramatic; however, if the tracheostomy is allowed to close at night, there is usually an immediate resumption of the sleep-apnea syndrome. Unlike severely symptomatic patients, mildly symptomatic patients may not require treatment.

Disordered breathing during sleep in patients with COPD can lead to life-threatening arterial oxygen desaturation and may contribute to chronic cor pulmonale. Arterial oxygen desaturation can be detected by nocturnal monitoring with an ear oximeter. Although not firmly established, the use of low-flow (1 to 2 liters per minute) oxygen during sleep has been recommended by many authorities because it benefits some COPD patients and usually has no obvious adverse effects.

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EDITORIALS

Of Job Actions and Such

THE RECENT air traffic controllers' strike somehow goes against the grain, much as do strikes and job actions by physicians, nurses or other health professionals when these occur. Perhaps this is because in both instances the health and safety of persons are put at risk by a relative minority for their personal gain, although the reasons are usually couched in euphemistic terms such as overwork or fatigue, or other reasons for inability to perform effectively in the public or patient interest. Leaving aside the issues of the legality of the air controllers' strike or their mass repudiation of a condition of employment they had each agreed to individually, this relatively small segment of the nation's population has sought to hold a much larger segment of the nation in economic hostage and to risk public safety in the air space to gain their special ends. Health professionals have not yet gone this far, although they are also essential when the health and safety of persons or the public are at risk, as in a hospital. And it is to their credit that health professionals have always made provision to maintain basic emergency care during their strikes and job actions, and by so doing have diluted the potential strength of their job actions.

Many things are changing as our society becomes more technologically complex, its people more technologically specialized, and the whole more technologically and therefore more economically interdependent. Specialization within this growing complexity has given rise to special interest groups which by definition must be minorities seeking to advance their own particular interests within the framework of the interdependent majority or whole. As complexity has continued to increase many such special interest groups have become more organized and more effective in advancing their cause. One can easily watch the growing importance and effectiveness of many of them in the political arena. Then, because interdependence increases along with specialization, each special interest group becomes a yet more essential cog in the machinery of the interdependent whole, with the result that its power, through strikes or job actions, to disrupt and damage the interdependent whole also increases. And indeed there is evidence that this can be and has been increasingly hurtful in the competitive world in which we as a nation now find ourselves.

A real question is at what point does costly disruption, or real danger to the health and safety of persons or the public, become too counterproductive from the standpoint of the majority, or society as a whole? Can we any longer afford the hurt and cost of strikes and job actions for the special interest of minority groups against the majority or the interdependent whole? Could it be that this is a tool or process that is beginning to outlive its value to our society now that the world is becoming more complex and competitive? It would seem that there must be some more civilized way for special groups with special interests to make their need, if not their greed, known to the majority, and be treated fairly. Considering what lies ahead for medicine and health care, it may not be too soon for the health professions to seek some better and less disruptive alternative to traditional strikes and job actions, which also go so much against the grain, where the health and safety of the public are concerned.

—MSMW

Classification of Malignant Lymphomas

ELSEWHERE IN THIS ISSUE is the Medical Progress article "Malignant Lymphomas: Cell Surface Markers and Advances in Classification" by Dr. James A. Strauchen.

The non-Hodgkin's lymphomas have been a source of confusion and controversy for both clinicians and pathologists for decades. The approach of Rappaport, published initially in the mid-1950's,[1] gave a spark of enlightenment, and it was appreciated finally in the early 1970's for helpful clinical correlation only after a lengthy period of gestation. Its major contribution was the demonstration that lymphomas exhibiting nodular

cellular proliferations were less aggressive and had longer median survival than those of the same cytologic type with diffuse histologic patterns.[2] The concept of Rappaport, however, did not relate the nodular proliferations of lymphoma cells to follicles but identified twice as many cases with a favorable prognosis as the follicular lymphoma.[2,3]

In the early 1970's Lukes and Collins presented a functional or immunologic approach to the malignant lymphomas, attempting to relate these disorders to the explosive developments in immunology of the 1960s.[4] Lymphomas were related to the T cell and B cell systems and lymphocyte transformation. A multiparameter technical approach, including immunologic surface marker studies, was presented for the redefinition of these disorders. A follicular center cell concept also was proposed by Lukes and Collins as a basis for their approach in which the follicular center was considered a site of B cell transformation.[4,5] According to this concept, the small B lymphocyte under antigenic stimulus evolved through cleaved cell stages to a noncleaved cell and eventually moved out of the follicular center as a B-immunoblast, the fully transformed B-lymphocyte and percursor of the plasma cell. Small and large cleaved cells were identified as the marker cells of normal follicular centers and the small and large noncleaved as the dividing cells of the follicular center.[4,6] Lymphomatous counterparts of each of these follicular center cells with varying frequency of follicle formation were identified and have distinctive clinical behavior and survivals.[7,8] It was proposed that nodular lymphomas were lymphomatous follicles composed of follicular center cells (FCC) with either cleaved or noncleaved FCC predominating.[1] At the time of the early publications of Lukes and Collins, before multiparameter studies, it was uncertain how many T cell and B cell subtypes ultimately would be identified. However, three predictions were made: (1) Lymphomas of large cells principally involved transformed lymphocytes of T cell and B cell types and, rarely, genuine histiocytes; (2) the nodular lymphomas of Rappaport were lymphomatous follicles composed of follicular center cells, and (3) lymphomas essentially were subtypes of the T cell and B cell systems. Our multiparameter studies from the intervening years have confirmed all of these predictions[9-12] as well as numerous investigators cited by Strauchen and summarized in a number of reviews.[13-15]

Initially, there were two strong candidates for T cell subtypes, the cerebriform cell of mycosis fungoides and Sézary's syndrome and the convoluted lymphocytic lymphoma which was frequently associated with mediastinal masses, most commonly observed in teenagers and young adults who often developed acute lymphocytic leukemia (ALL).[16] The convoluted T cell lymphoma/leukemia, also known as lymphoblastic lymphoma,[17] has become a well-recognized and generally accepted entity that interrelates with T cell ALL. Two other subtypes seemed likely, the small lymphocyte of T cells (T cell CLL [chronic lymphocytic leukemia]) and T-immunoblastic sarcoma, both of which were subsequently confirmed and added to the classification of Lukes and Collins[10,11] Finally, a fifth type, the lymphoepithelioid cell, which is the distinctive T cell lymphoma previously included in the heterogeneous group of disorders of the so-called Lennert lesion, has been established in the study of a small group of cases.[11,18]

Using a continually expanding variety of techniques, many of which Strauchen has discussed, including immunologic surface marker studies, cytochemistry, electron microscopy, immunoperoxidase, monoclonal antibodies, cell kinetics, numerous investigators, including ourselves, have established the malignant lymphomas as neoplasms of the immune system involving principally T cell and B cell types and rarely of histiocytes as macrophages. The lymphoma of large cells, previously known as reticulum cell sarcoma of histiocytic lymphoma, principally involves transformed lymphocytes of T cell and B cell types. The diffuse lymphomas of the past have been shown to be heterogeneous groups and included both T cell and B cell types which blurred clinical and morphologic distinctions. As a result of multiparameter studies, numerous clinical, morphologic and immunologic entities are emerging, possibly as many as 10 to 12 in all. Of great importance is the appreciation that malignant lymphomas are composed of cytologic types which are counterparts of normal cells and represent defective immune cells with varying degrees of abnormality. They, thus, migrate and home to the respective T cell and B cell sites and function, to varying degrees, like normal cells. Thus, as the entities are studied in detail, it is apparent that the initial presentation, distribution and frequency of tissue involvement reflect, to some extent, the normal counterparts of the lymphomatous cells.

Lymphomas develop, as Strauchen has indi-

cated, in the T cell and B cell lineage either at various levels of development or in the effector cells. Lymphomas of immunoblasts in the T cell and B cell systems represent the deviation from the developmental concept since they represent the dividing cell or the proliferative state of the effector cell rather than a precursor cell in the system as the term "immunoblast" might suggest. Thus, immunoblastic sarcoma of T cell or B cell type may be encountered either in the initial presentation as a highly aggressive process or in a late stage having evolved from a low grade or effector type cell, such as chronic lymphocytic leukemia of B cell type, when it changes to a large cell, the B immunoblast in the entity known as Richter's syndrome. We have observed immunoblastic sarcomas developing in many of the small subtypes of the T cell and B cell system. In addition, B-immunoblastic sarcoma develops, in our experience, in a wide variety of abnormal immune states, such as immunoblastic lymphadenopathy, Sjögren's syndrome and systemic lupus erythematosus (SLE)-like disorders.[19] Appreciation of the phenomenon of lymphocyte transformation thus has helped us understand that the appearance of a second cytologic type of lymphoma is most likely a change in the kinetic state, from low to high grade, rather than the occurrence of a genuinely different second type of lymphoma previously designated as a composite lymphoma. The occurrence of a second lymphoma, such as immunoblastic sarcoma in Hodgkin's disease, also may represent clonal evolution from the same defective clone (according to unpublished data ["Association of Hodgkin's Disease With Immunoblastic Sarcoma of B Cell Type: An Immunohistological Study"] by B. Falini, I. DeSolas, W. Fish and C. R. Taylor), but further studies are needed to clarify this issue.

The dramatic development of modern immunology since the 1960's has provided a sound basis for the understanding of the immune system and its neoplasms, the malignant lymphomas and related lymphoid leukemias. The immunologic investigations have put at our disposal a technical armamentarium for the redefinition of the cytologic types and permitted precise characterization. For the morphologist, these techniques have allowed greater insight and a new appreciation of the significance of the morphologic features, and permitted the recognition of the heterogeneity of the cytologic types of the past, such as histiocytic lymphoma and poorly differentiated lymphocytic lymphoma of Rappaport, as well as childhood acute lymphocytic leukemia (ALL). Using multiparameter studies, we have investigated over 800 cases of non-Hodgkin's lymphomas and related leukemias and discovered that the morphologic features in carefully collected and properly processed histologic material can be an effective predictor of the T cell and B cell subtypes by an experienced hematopathologist.[12] Numerous technical problems in the application of the multiparameter procedures, together with biologic variations of lymphoma cells, render the effectiveness of the techniques far from perfect and inferior in our hands to the morphologic identification of cytologic types.[10-12] The use of the recently developed, highly specific monoclonal antibodies produced by the hybridoma system offers great promise in the future of elevating the lymphoma cell characterization to a high level of sophistication. Our experience with monoclonal antibodies on both cell suspensions and frozen sections thus far indicates that this approach is not free of problems, and it will be some time before both their precise role and effectiveness will be established.

The new formulation for pathology of malignant lymphomas, resulting from a study sponsored by the National Cancer Institute, discussed by Strauchen, is not intended as a new classification, but as a basis for translating the major classifications in use around the world. It is unfortunate that a consensus could not be achieved on an immunologic classification with T cell and B cell subtypes since this serious omission renders the formulation for pathology outmoded at the time of publication. It is, indeed, a remarkable and unparalleled study, and it is unfortunate that this final and most important step could not be achieved. Unquestionably, the new formulation will provide an improved understanding of the relationship of the various classifications and put to rest much of the controversy and debate. The clinicopathological correlation data, accumulated from the enormous statistical studies, provide extremely valuable information for comparison studies from medical centers around the world.

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Malaria: A Great Relatively Neglected Disease

LAST YEAR in an address to an international meeting on malaria, I spoke about the "great neglected diseases of mankind"—diseases that are vast in number (hundreds of millions of cases at least) and neglected in terms of scientific interest and financing. I was not only informed, in a slightly offended tone of voice, that malaria is not a neglected disease, but I had to agree that it was in relatively good shape. For instance, it was one of the six chosen diseases of the Tropical Diseases Research Programme of the World Health Organization (WHO) and, among those, it is funded at two to three times the level of any of the others. At present, this equals all of $4 million a year. This is particularly poignant in view of the remark of a Trustee of the Rockefeller Foundation, Richard W. Lyman (now its President), when enthusiastically informed of the WHO Programme several years ago: "Perhaps we should call them the great relatively neglected diseases of mankind."

Total global support for research in all of these diseases is about $60 million per annum. Compare this with cancer: with a prevalence of nearly 10 million cases worldwide, cancer research receives $40 million from the American Cancer Society alone, plus another $1,000 million a year from the National Institutes of Health. The National Institute of Allergy and Infectious Diseases' total budget for all parasitic infections, most of which are great neglected diseases, was about $18 million this year.

Malaria is unquestionably a great disease—300 million cases annually, with 1 million childhood deaths in Africa alone. Many think it is the greatest single health scourge of mankind. Nevertheless, the huge global effort to eradicate malaria has been abandoned. In the words of the Director General of the World Health Organization, "we have thrown in the towel." An impossible dream had not been achieved. Immediately after World War II there were two exceedingly powerful new tools, DDT (a uniquely long-acting insecticide) and chloroquine (a nontoxic prophylactic and curative drug). The time appeared ripe for eradication and, in subsequent years, the accomplishment was great. But now mosquitoes in most endemic areas are resistant to DDT, and in entire regions such as Southeast Asia parasites are more than 80 percent resistant to chloroquine. Sulfadoxine pyrimethamine (Fansidar), another excellent new drug, now shows 20 percent resistance. Quinine is again in wide use.

The incredibly versatile malaria parasite is now undergoing a resurgence globally. Sri Lanka, a large island, had almost eradicated malaria, with about one recorded case per month. Twelve years ago, in a matter of months, the incidence of malaria increased to more than a half million cases and it remains at that annual level today. The vast land areas and populations of India are steadily being invaded by the mosquito and the parasite; from 100,000 cases annually in the early 1960's to 30 to 50 million today. Malaria has returned to Europe, causing epidemics in the rural areas of Western Turkey. It is another one of the many

problems plaguing poor little Haiti. American tourists are still dying of malaria.

Malaria is a significant component of the Great Neglected Diseases Program of The Rockefeller Foundation, in which we have proselytized among outstanding scientists in order to engage them in research on the diseases of the developing world. Conversions have been surprisingly simple because of the humanitarian concerns of many of the scientists and their perception of a unique opportunity provided by systems of known etiology where relatively rapid breakthroughs could be accomplished. These problems are being attacked by the Tropical Medicine Unit at Oxford under David Weatherall, the joint Immunoparasitology Unit at Stockholm and Uppsala Universities under Peter Perlmann and Hans Wigzell, and similar units at Harvard University under John David, and the Walter and Eliza Hall Institute in Melbourne under Graham Mitchell. Victor and Ruth Nussenzweig, the latter an outstanding malariologist, at New York University are working on it, as well as Anthony Cerami at Rockefeller University, Anil Jayawardena at Yale and Rupert Schmidt-Ullrich at Tufts. Immunology is a major discipline involved, although some imaginative biochemical and pharmacological pathways are being pursued.

What is the hope? Marcel Hommel, supported by The Rockefeller Foundation at the Pasteur Institute in Paris and now at Harvard, has presented a lucid picture of malaria in his paper on immunity and prospects of vaccination, elsewhere in this issue. These prospects are bright because of several methodological breakthroughs in the last few years. The in vitro cultivation of *Plasmodium falciparum* was an important and heartening event. Most exciting, however, has been the adaptation of the new hybridoma technique with which protective antibodies have been produced in the test tube against all three stages of the malaria parasite: the mosquito-injected, liver-infective stage (sporozoite), the multiplying, red blood cell-infective stage (merozoite) and the sexual, mosquito-infective stages (gametocytes). Using highly specific hybridoma antibodies, relevant antigens for vaccines may be identified, characterized and produced either chemically or via genetic engineering. This, plus exciting new work on adjuvants, suggests the probability of a vaccine in the foreseeable future. These projects would be enhanced even further if research on malaria could be financed in some small degree proportionate to its importance. This would in turn easily involve the concerned global community of scientists. In addition, research on insecticides and chemotherapeutic agents, particularly depot preparations, should be strongly fostered. Since all biomedical research is an interlocking continuum, studies of this complex chronic infection should enhance our knowledge of diseases, such as cancer, that are of concern to both the developed and developing countries.

But we must not forget the other great neglected diseases: the diarrheas and pneumonias that kill 10 to 15 million children a year; schistosomiasis, a chronic and potentially lethal infection of 200 million people, spreading through irrigation; sleeping sickness, the scourge of 1 million people and tens of millions of cattle in Africa; filariasis, afflicting 300 million persons and bringing the miseries of elephantiasis and river blindness; ascariasis, an infection with footlong intestinal worms that afflicts 1,000 million people, and so on.

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The Doctor and the Computer

"A Computer Terminal Program to Evaluate Cardiovascular Functional Limits and Estimate Coronary Event Risks," by Robert A. Bruce and his co-workers, appears elsewhere in this issue. These investigators from Seattle are developing a system that allows physicians to learn from the experience of other doctors and patients through the use of a computer. Within minutes of the completion of an exercise test the measurements from the test are translated into prognostic estimates based on experience from thousands of other patients. They have appreciated that the computer can be used to store medical experience in an orderly fashion so that it can be related to an individual patient as needed. This type of approach portends a revolution in medical knowledge that will change the education and practice of physicians.

In our society the two primary goals of physicians are to prolong life and to improve the quality of life of each patient. The quality of life may be improved by curing the disease, ameliorating the symptoms of the disease, or by informing the patient of the prognosis (whether good or bad)

and helping the patient adjust to the information. How does a physician know that a specific therapy will accomplish these goals? Often, in acute, short-term illnesses, such as pneumonia, the effects of therapy are obvious. However, in chronic diseases, such as coronary artery disease, the effects of therapy are much more difficult to gauge. Before the therapy can be judged, an understanding of the likely outcome of the disease without the therapy must be known. Yet, we often lack a clear understanding of the natural history of chronic disease.

Traditional medical education is concerned with the placement of disease into broad diagnostic categories. Educational methods such as lectures, textbooks and journal articles most often deal with these broad categories of disease states. Patients and doctors, however, are not concerned as much with disease states or diagnostic categories, but with the likely outcome of the disease process in a given patient. Within a diagnostic category such as coronary artery disease, the outcome is dependent on a variety of factors such as the contractile state of the left ventricle, the location and severity of atherosclerotic lesions, the degree of angina, and the ability of the patient to adapt to the disease, both physiologically and psychologically. Before the advent of the computer, no educational medium could consider this large number of factors, so the care of the individual patient largely has been left to "clinical judgment."

The computer is a tool that is designed to consider multiple factors. By pooling their individual results of treating patients into a central data bank, physicians are able to increase their clinical knowledge by way of the experience of others. In essence, in the Seattle experiment physicians receive continuing education about the natural history of coronary artery disease in a manner that is applied to individual patients each time an exercise test is done.

As such systems evolve, several problems will have to be addressed. First, the scope of the data included in the patient profile will have to be increased. For example, in patients with no clinical manifestations of heart disease, more precise definition of the risk factors may allow for more accurate predictions. On the other hand, in patients with symptomatic heart disease, a better description of the resting electrocardiogram and the details of the patients' chest pain syndromes may be at least as important as the exercise descriptors. As such systems are able to take into account more factors, the predictability will certainly improve.

Second, statistical methodology will have to be tested so that the model that produces the most accurate prediction can be used. The Seattle group has used a logistic function that considers risk at fixed times. Another promising approach is provided by the Cox model, which allows one to study the time course of the development of untoward events. Physicians will have to insist on the testing of the various models on patient groups that are independent of those for which the models were developed. Such testing will help to identify the most appropriate model. Further, it will also help to identify patient descriptors that enter the model because of some unusual distribution of characteristics in the original patient sample but that probably will not help to make accurate predictions. For example, in the report from Seattle, the *height* of the patient probably will not stand the test of time as the fifth most important predictor of survival in patients with symptoms of coronary disease.

Third, attention must be devoted to the manner of presentation of the prognostic estimates. A format that is easily understood by both patients and physicians will have to be developed.

Fourth, the implementation of such systems will have to include a mechanism for updating the estimates to take into consideration changes in the population and in technology. In coronary disease, it is clear that the results of surgical therapy and medical therapy are changing. Therefore, a mechanism must be devised for continuing to collect data on a sample of patients as the Seattle group has done.

Finally, physicians must be as aware of the limitations of such a system as they are of any other technology that they employ in the evaluation of patients. At present, these limitations are most apparent when treatment comparisons are made. In the Seattle study, patients with left ventricular dysfunction (based on noninvasive criteria) who had surgical intervention fared better as a group. However, the medically treated patients had a mean ejection fraction of 49 percent compared with 58 percent in the surgically treated patients. Because left ventricular function is the most important predictor of short-term survival in medical or surgical therapy of coronary disease, the difference in survival is probably due to the better left ventricular function in the surgical

patients rather than to the operation itself. When patients have not been placed randomly into treatment groups, great care has to be taken to insure that differences in outcome that result from patient selection are not inappropriately attributed to the treatment.

In summary, the Seattle project represents an implementation of an approach that illustrates how doctors and patients can gain from carefully collected and computerized clinical experience. Predictions were that many such projects would be flourishing by 1980. The time course has been slower because of the difficulty of characterizing the complexity of chronic illness rather than because of problems with computer technology. In the future, data banks will provide a reference library for each patient with chronic disease. Proper interpretation and use of computerized data will depend as much on wise doctors as any other source of data in the past.

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CASE REPORTS

Refer to: Johnson WM: Fatal disseminated coccidioidomycosis following an intestinal bypass operation for obesity. West J Med 135:324-326, Oct 1981

ABBREVIATIONS USED IN TEXT

CF = complement fixation
EEG = electroencephalogram

Fatal Disseminated Coccidioidomycosis Following an Intestinal Bypass Operation for Obesity

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A VARIETY of medical complications following intestinal bypass operations for morbid obesity have been reported.[1] Electrolyte depletion, malnutrition and hepatic insufficiency are serious problems; other complications include renal stones, polyarthritis and loss of hair. Fifteen patients have been reported with tuberculosis after intestinal bypass operations.[2-10] Two cases of pulmonary histoplasmosis occurred following jejunoileal bypass,[11] and a case of localized endobronchial coccidioidomycosis, which occurred three years following a jejunoileal bypass operation, has been reported.[12]

The present report of disseminated coccidioidomycosis following an intestinal bypass operation supports opportunistic infection as a potential complication of such procedures.

Report of a Case

A 39-year-old woman, a resident of Arizona since 1973, had a jejunocolic bypass operation for morbid obesity in June 1968 in Philadelphia. Her preoperative weight was 143 kg (315 lb). A total of 71 cm (28 in) of proximal jejunum were anastomosed end-to-side to the transverse colon. Her weight stabilized at 61 kg (135 lb) following initial weight reduction. In 1972 a liver biopsy study showed no abnormalities. She received periodic parenteral therapy with vitamins A, D and K, folic acid, and iron dextran for malabsorption that was manifested by a macrocytic anemia, elevated prothrombin time, low serum carotene levels, hypoalbuminemia and episodes of night blindness (which responded to parenterally given vitamin A).

In January 1975 the patient had a nonproductive cough and low-grade fever. Findings of a roentgenogram of the chest were within normal limits. In March 1975 abscesses developed in the subcutaneous tissues of the anterior chest wall, left breast and right upper quadrant of the abdominal wall. Incision and drainage were carried out for the first two abscesses, and *Coccidioides immitis* organisms were reported on culture. (*C immitis* is a soil fungus that causes coccidioidomycosis. The infection is endemic in some arid regions of the southwestern United States.) A coccidioidin skin test (1:100) was negative, and the coccidioidal complement fixation (CF) titer was 1:32. The patient declined therapy for disseminated coccidioidomycosis with amphotericin B, against the recommendations of several physicians.

In April 1975 the serum CF titer had increased to 1:128. Latex fixation and immunodiffusion tests for coccidioidomycosis were positive. In May 1975 she finally agreed to amphotericin B therapy as an outpatient. However, after experiencing chills following intravenous administration of the first 1.0 mg of amphotericin B, she declined further therapy. She had pain in the left leg, and roentgenograms (including tomography) showed an abnormality consistent with coccidioidal osteomyelitis of the left distal tibia. A week later she was admitted to hospital following seizure activity. A brain scan suggested poorly defined small foci in the left frontal, left parietal and right occipital regions and was consistent with multiple

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inflammatory foci. Findings of a skull film were unremarkable, and an electroencephalogram (EEG) showed a focal irregularity in the left frontotemporal region. A lumbar tap showed an opening pressure of 210 to 250, and examination of the cerebrospinal fluid showed an elevated protein level of 71 mg per dl, 4 leukocytes (4 lymphocytes) and a CF titer of 1:2. The possibility of early coccidioidal meningitis was suggested; however, the patient declined amphotericin B therapy and was discharged.

In June 1975 a coccidioidin skin test (1:10) was positive at 15 mm. The patient agreed to return to hospital, and intravenous amphotericin B therapy was started after a spinal tap showed no evidence of meningitis. A repeat brain scan was interpreted as within normal limits. Focal EEG abnormalities persisted in the left frontotemporal region. During the second hospital week the patient became lethargic and complained of headache. On the 15th hospital day she became unresponsive; brain stem herniation was diagnosed, and the patient died. An autopsy was not done; however, the final clinical event was considered brain stem herniation secondary to an expanding coccidioidal brain abscess. A total of 505 mg of amphotericin B had been administered intravenously during the patient's stay in hospital, and roentgenograms of the chest were consistently within normal limits.

Comment

This patient underwent a jejunocolic shunt, an intestinal bypass procedure initiated in 1956 for treatment of severe, morbid obesity.[13] However, the use of the jejunocolic bypass operation has been terminated because of intolerable metabolic complications that develop following the procedure. Subsequently, jejunoileal bypass procedures have been done, with associated nutritional and metabolic complications.

Of the 15 reported cases of tuberculosis following intestinal bypass operations, 13 have occurred following a jejunoileal bypass; in two cases the type of intestinal bypass procedure was not specified.[6] Only 3 of 15 patients had pulmonary tuberculosis.[4-6,8] Tuberculosis of the lymph nodes was diagnosed in eight patients,[2-4,7,9,10] hepatic granulomas were present in two patients[7] and skeletal tuberculosis was diagnosed in one patient.[6] In one patient tuberculous peritonitis developed.[10]

Malnutrition is a recognized risk factor for the development of infections.[14] Cell-mediated immunity has been shown to be depressed in both animals used in experiments and in humans with protein-calorie malnutrition.[15-16] In children with malnutrition, tuberculin sensitivity is diminished following both BCG (bacillus Calmette-Guerin) vaccination and clinical tuberculosis.[17,18]

Coccidioidomycosis has been recognized increasingly as an opportunistic infection.[19] Disseminated coccidioidomycosis is frequently associated with an absent or diminished reactivity to coccidioidin,[20] as occurred in this patient. Further, it has been shown that cell-mediated immunity is essential to resistance to experimental infection with *C immitis* in mice.[21] The nutritional complications that followed the intestinal bypass operation in this patient may have suppressed cell-mediated immunity, thus permitting the dissemination of *C immitis*.

Summary

In a 39-year-old woman, disseminated coccidioidomycosis with subcutaneous abscesses, bone lesions and neurological complications developed seven years after a jejunocolic bypass operation for morbid obesity. A review of the literature showed 15 cases of tuberculosis, 2 cases of histoplasmosis and 1 case of coccidioidomycosis following intestinal bypass operations. Depression of cell-mediated immunity as a nutritional complication of intestinal bypass procedures is a likely factor in such opportunistic infections. Disseminated coccidioidomycosis may be a potential complication of such surgical procedures in geographic areas where coccidioidomycosis is endemic.

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Refer to: Kaplan AL, Huerta AR, Chiou SJ: Rhinocerebral mucormycosis. West J Med 135:326-329, Oct 1981

Rhinocerebral Mucormycosis

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MUCORMYCOSIS, an infection caused by fungi from the order Mucorales, was considered universally fatal until the late 1960's.[1] Since then increasing numbers of cases have been reported[1-4] in which early diagnosis and aggressive treatment have resulted in better outcomes. Increasing incidence of mucormycosis correlates with the advent of immunosuppressive drugs. Predisposing factors extend beyond antimetabolites and include severe burn states, leukemia, lymphoma, renal disease, sepsis, severe dehydration and prolonged steroid use.[5,6]

The most common associated disease reported is diabetes mellitus—both controlled and uncontrolled.[7] Mucormycosis may have a predilection for the acidic pH, high temperature, high glucose content or a combination of these in patients with diabetic ketoacidosis. Some studies indicate that leukocyte function and local tissue accumulation of granulocytes are impaired during ketoacidosis, thus decreasing natural immunity. However, the mechanism is still unknown.[6]

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ABBREVIATIONS USED IN TEXT
BUN = blood urea nitrogen
CT = computed tomography

Mucormycosis usually presents in any one or combination of four types: rhinocerebral, pulmonary, systemic and gastrointestinal, although fungi of a related order may cause other miscellaneous disorders. The rhinocerebral form constitutes approximately 50 percent of all cases of mucormycosis and greater than 75 percent of cases in patients with diabetic ketoacidosis.[6] The disease is usually acute and fulminating. Early diagnosis and aggressive therapy, including treatment of the underlying systemic disease, surgical debridement and administration of amphotericin B, are essential in the management of rhinocerebral mucormycosis. Clinicians should consider this diagnosis when confronted by even the earliest signs and symptoms.[8]

We present the case of a patient admitted to hospital with obvious diabetic ketoacidosis and findings that suggested mucormycosis of the right eye. This latter condition was correctly diagnosed early in her hospital course. Immediate and aggressive combined treatment with amphotericin B and surgical debridement led to the resolution of the mucormycosis.

Report of a Case

A 52-year-old woman was seen with complaint of a severe headache and difficulty in breathing. She was agitated and disoriented. In 1974 she had been treated with radioactive iodine for Graves' disease. At that time she was thought to have "possible latent chemical diabetes mellitus" but she had been lost to follow-up.

On physical examination the patient was noted to be obese. There was evidence of Kussmaul respirations and an odor of acetone was apparent. Pulse was 118 and respirations 36 per minute, temperature was 37°C (98.6°F) and blood pressure was 218/122 mm of mercury. The patient's right eye was proptotic with periorbital edema, redness and conjunctival chemosis. Results of the physical examination were otherwise unremarkable.

Laboratory data confirmed the presumptive diagnosis of diabetic ketoacidosis. Pertinent findings included the following: analysis of urine

showed glycosuria of 4+ and substantial acetonuria; random blood glucose measured 678 mg per dl, with substantial ketonemia in the blood. Arterial blood gas determinations, with the patient breathing room air, showed a pH of 7.02, partial pressure of oxygen 151 and partial pressure of carbon dioxide 9 mm of mercury, and bicarbonate 2 mEq per liter. Electrolyte values included sodium 136, potassium 4.6 and chloride 103 mEq per liter; carbon dioxide content was 3 mM per liter. Blood urea nitrogen (BUN) was 17 mg per dl. An x-ray study of the chest showed no abnormalities.

Intensive treatment with intravenous insulin therapy, hydration and electrolyte replacement resulted in rapid improvement.

Despite general improvement, the patient's orbital and facial findings progressed with development of complete right-sided ophthalmoplegia, increased proptosis, chemosis, periorbital edema and evidence of a VII cranial nerve palsy. Funduscopic examination showed slight haziness of the right optic disc margins. A roentgenogram showed haziness of the right maxillary antrum and right frontal sinus. Treatment for presumed rhinocerebral mucormycosis was initiated, pending planned maxillary sinus biopsy. The patient was given 10 mg of amphotericin B intravenously the day after admission. In addition, to cover the possibility of orbital cellulitis, she was treated with intravenously given gentamicin, penicillin and methicillin.

By hospital day 4, the patient's medical condition was stable. However, her right pupil was fixed and dilated, she could see hand movement only and a right fifth nerve palsy had developed.

At operation, the right maxillary antrum was stripped of mucosa with minimal bleeding. The biopy specimen contained fungus with nonseptated hyphae in the tissue and invading blood vessels. Subsequently, organisms of the genus *Mucor* but no bacteria were grown from this specimen.

Amphotericin therapy was continued with alternate-day doses of 40 mg and 50 mg. The patient experienced side effects including chills, fever and agitation, which necessitated treatment with acetaminophen, diphenhydramine and diazepam before amphotericin B administration.

On day 6 the patient had no light perception in her right eye. A computed tomographic (CT) scan of the head showed an abscess involving the orbit and the maxillary pterygoid fossa but no extension into the brain.

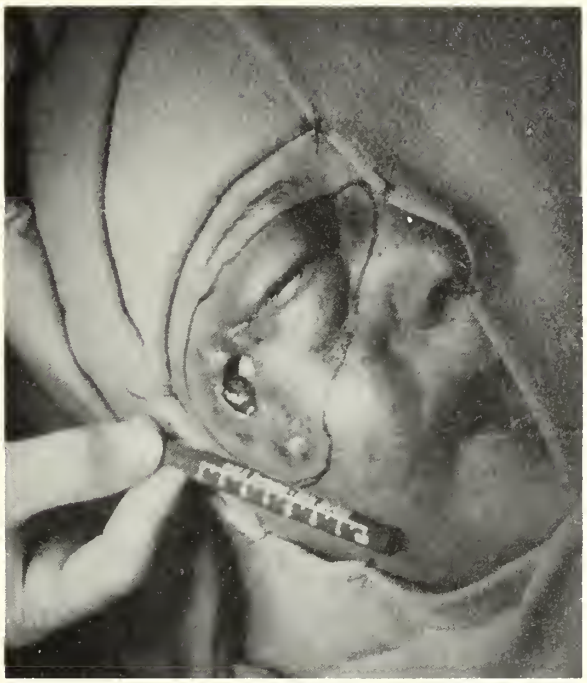

Figure 1.—Patient just before extensive facial debridement (second surgical procedure). Note marking pen lines indicating limit of debridement.

On day 8 the patient's right eye was enucleated and a right ethmoidosphenoidectomy was done. The tissue removed was necrotic and, again, minimal bleeding was noted during the operation. The orbit was irrigated with 1 mg per ml of amphotericin. Fungus was detected in the tissue that was removed. At this time, a Broviac catheter was placed for long-term administration of amphotericin.

Following the operation, there was considerable improvement in both physical and mental status of the patient. The swelling on the right side of the face became fluctuant, and aspirated purulent material grew both *Mucor* and *Klebsiella* organisms. Despite ten days of drainage, adequate antibiotic coverage and administration of more than 0.5 gram of amphotericin, a repeat CT scan showed thinning and erosion of the posterior walls of the maxillary and ethmoid sinuses.

Figure 1 shows the patient just before the second surgical procedure. Pen lines indicate where the extensive debridement was done, which extended to the dura mater and the hard palate and included removal of the right orbit. All tissue was necrotic and on microscopic examination evidence of fungus was found.

The patient did well postoperatively but was left with a large defect of the right side of the

Figure 2.—Patient approximately six months after last surgical procedure. Note excellent condition of lateral skin graft.

face, which communicated with the oropharynx. The optic stump showed traces of compromised tissue. Administration of amphotericin was continued in dosages of 25 to 40 mg every second to third day, with careful monitoring of hematopoietic and renal function as well as magnesium and phosphorus levels. Amphotericin was not given on days when serum levels of creatinine were greater than 2.5 mg per dl. Drainage containing *Klebsiella* organisms continued and, after a ten-day course of chloramphenicol, antibiotic therapy was discontinued.

Five weeks later a prosthetic palate was inserted. Eight weeks after admission, the patient underwent her last surgical procedure. An area of necrosis of the sphenoid bone was removed, and a split-thickness skin graft from the right thigh was placed in the anatomic defect. There was no evidence of necrosis postoperatively, and a CT scan showed no further vascular or soft tissue involvement. Amphotericin therapy was continued on the schedule already mentioned.

The patient continued to improve. At the time of discharge, 17 weeks after admission, her diabetes was controlled by diet alone, and all routine laboratory values were normal. Eight weeks later she showed no evidence of mucormycosis.

Figure 2 shows the patient approximately six months after the last surgical procedure, including the excellent condition of the lateral skin graft. The patient will receive an orbitofacial prosthesis to improve the cosmetic appearance of the wound site.

Discussion

Zygomycotina (phycomycetes), a class of nonseptated fungi, is made up of two orders known to cause disease in humans. *Mucor, Rhizopus,* and *Absidia,* three genera of the order Mucorales, are considered the causative organisms of mucormycosis. The order Entomophthorales may cause dermatitis as well as granulomatous nasal infections in normal hosts. These fungi are ubiquitous and can be found in soil, manure and debris.[3,5,7] They are aerobic in metabolism, and although humans have a natural resistance to the organism, they can cause disease in compromised hosts.

The fungi inflict damage by penetrating the arterial walls and stripping the intima from the media. This in turn leads to both invasions and occlusion of the lumen and gives rise to the characteristic findings of thrombosis, infarction and necrosis.[6,9]

The earliest suggestion of mucormycosis may be facial pain that is severe and not in keeping with the physical signs or borderline haziness of the roentgenogram.[2-4] Subsequently, other signs and symptoms develop, including facial swelling, chemosis, proptosis, loss of vision, cranial nerve damage, diplopia, bulging masses in the palate or nasal turbinates, ulcers in the palate, sinusitis or fever.

Diagnosis of rhinocerebral mucormycosis is made either by a successful culture of infected tissue or microscopic identification of the nonseptated fungus in thick tissue preparations stained with hematoxylin and eosin or silver methenamine.[7] Results of routine laboratory examinations are variable and nondiagnostic.[2,4]

Management of infection begins with the control of the underlying disease process. This enables the host to regain his or her natural resistance. Surgical debridement of all infected tissues, which may be extensive, should be done. Therapy should also include treatment with the fungistatic antibiotic agent amphotericin B.[9-11] A test dose may be given followed by doses of approximately 1

mg per kg of body weight per day to a recommended total cumulative dose of 2.5 to 3.0 grams. Side effects are multiple. The most serious is nephrotoxicity, which is dose-related and usually reversible if amphotericin B is not administered on days when BUN values are 50 mg or higher[10] and creatinine serum level measure 3.0 mg per dl or greater. Alternate-day therapy helps in decreasing nephrotoxicity.

Other side effects include nausea and vomiting, chills, headache, anemia, hypokalemia and hypomagnesemia, fever and phlebitis. Use of steroids given intravenously, or diphenhydramine or prochlorperazine given intramuscularly 60 minutes before giving amphotericin B helps to diminish some of these side effects. Use of anticoagulant drugs is not advocated, and the use of systemic steroids and antibiotics should be judicious.

Conclusions

A patient with diabetic ketoacidosis, headache and a proptotic eye (such as our patient) should immediately be suspected of having mucormycosis, although other entities such as suppurative sinusitis, orbital/periorbital abscess, tuberculosis, rhinosporidiosis, rhinoscleroma, cavernous sinus thrombosis, malignancy, internal carotid artery aneurysm and cholesteatoma of petrous apex may be considered.

Treatment with amphotericin B should be instituted promptly in the hope of preventing further spread of the infection. The reversible nephrotoxicity associated with amphotericin administration is usually dose-related, so that the drug may be stopped early with little fear of permanent renal damage, should the diagnosis be incorrect.[10]

While the patient's diabetes is being brought under control, plans for biopsy of affected tissue should be made. As soon as the diagnosis has been established amphotericin should be given in as high a dose as can be tolerated by the patient.[2,3,5,9] Monitoring of renal function, blood counts, and magnesium and potassium levels is important. The indwelling Broviac catheter seems to be well suited for long-term intravenous therapy without the need for repeated peripheral lines and with minimal risk of sepsis.

Not only will the tissues be infected with the *Mucor* fungus, but its predilection for invading blood vessels may result in thrombosis, vascular compromise and ischemic tissue. Both infected and gangrenous areas should be resected. In our patient, tissue was removed until adequate bleeding was encountered, on the assumption that the bleeding tissue would be normal.

Because recent reports have quoted survival rates as high as 85 percent,[5] rhinocerebral mucormycosis, particularly in patients with diabetes should not be thought of as the uniformly fatal disease it once was. Every attempt should be made to diagnose and treat the infection as soon as possible. Although this patient was left with substantial cosmetic deformity, she still has one functional eye, no evidence of cerebral involvement and no change in mental functioning.

Summary

Rhinocerebral mucormycosis, a fungal infection affecting diabetic patients and otherwise immunocompromised hosts, was considered fatal until the late 1960's. Since then, early diagnosis and aggressive treatment including intravenous amphotericin B administration and surgical debridement have led to more favorable outcomes. We present a patient admitted in severe diabetic ketoacidosis with initially subtle eye abnormalities. Early recognition of the infection allowed prompt initiation of treatment with intravenously given amphotericin. Fungal invasion into surrounding tissues and the vascular compromise typical of mucormycosis necessitated three extensive surgical debridements including complete orbital excision. The patient was left with significant cosmetic deformity, but no cerebral involvement, and one normal eye. It is therefore critical that clinicians consider the diagnosis of rhinocerebral mucormycosis in patients at risk when confronted by even the earliest signs and symptoms.

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Cimetidine and Cytopenia

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A NUMBER OF REPORTS have recently described cimetidine-associated granulocytopenia, some with documented bone marrow depression.[1-3] In addition, cimetidine-associated thrombocytopenia has been described.[4,5] Since the first widely used histamine H_2 receptor antagonist, metiamide, was withdrawn from clinical use because of related agranulocytosis, concern has arisen that cimetidine may also have adverse hematologic effects.

Review of the reported cases of cimetidine-associated cytopenia suggests that a prerequisite to this complication may be preexisting compromise of bone marrow stem cell reserves. However, there have been no specific experimental data pertaining to this hypothesis.

We describe two cases of cimetidine-related granulocytopenia, one accompanied by thrombocytopenia, and report the results of in vitro bone marrow tissue cultures and antibody detection studies carried out to attempt elucidation of the mechanism of cimetidine toxicity.

Reports of Cases

CASE 1. A 78-year-old white man was admitted to Cedars-Sinai Medical Center in February 1979 with stomatitis, perirectal ulcerations and fever.

Eight months earlier, chronic lymphocytic leukemia was diagnosed and was treated with chlorambucil (oral administration of 4 mg per day for five days and then 2 mg per day for five days) and prednisone. Thereafter, his leukemia required no further treatment. Four months later, he was admitted to hospital because of gastrointestinal hemorrhage. No bleeding site was found by either endoscopic or radiographic methods and intravenous vasopressin therapy successfully controlled the hemorrhage. He was discharged on a regimen of 300 mg of cimetidine given orally four times a day for presumed radiologically inapparent peptic ulcer disease.

A month later, in November 1978, exfoliative dermatitis developed. Biopsy of the skin lesions showed no leukemic involvement. Administration of prednisone, 60 mg orally every other day, was begun and the dermatitis resolved; however, discontinuation of treatment after a month resulted in recurrence of the dermatitis. Reinstitution of prednisone in the same dosage led to improvement. This treatment was gradually tapered and finally stopped several weeks before his admission to Cedars-Sinai Medical Center.

Three weeks before admission, the patient's cell count included the following: hemoglobin 13.3 grams per dl, hematocrit 39 percent and leukocyte count 12,700 per cu mm, with 31 percent neutrophils, 1 percent band forms and 68 percent lymphocytes; platelet count was 170,000 per cu mm.

During the three weeks before admission, he experienced oral discomfort, rectal pain and tenesmus. Fevers and sweats occurred during the two weeks before admittance to hospital. Ulcers of the tongue developed, and the patient experienced increasing difficulty in swallowing. During the week before admission, progressive weakness was noted. No easy bruising, bleeding or lymph node enlargement occurred. There was no history of recent respiratory infection, hepatitis, connective tissue disease or exposure to chemical toxins. He had taken no medications other than cimetidine and the recent course of prednisone.

Physical examination on admission showed a cachectic, dehydrated man. The temperature was 39°C (102.2°F). His skin was anicteric and showed mild exfoliative dermatitis on all four extremities. No lymph node enlargement was noted. The oral mucosa was clear, but on the tongue there were two exquisitely tender ulcers (each 1 cm in diameter), with yellow depressed centers and indurated borders. There was no enlargement of the liver or spleen. Rectal examination showed a 1-cm perianal ulcer with a yellow center and indurated border, a rectocutaneous fistula and induration of the rectal mucosa.

Laboratory data included the following: hemoglobin 12.9 grams per dl, hematocrit 37.2 percent, normal erythrocyte indices and leukocyte count

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3,200 per cu mm, with 1 percent neutrophils, 90 percent lymphocytes, 6 percent atypical lymphocytes and 3 percent monocytes; platelet count was 420,000 per cu mm. Prothrombin time, partial thromboplastin time, serum protein electrophoresis and creatinine values were within normal limits.

A bone marrow aspirate and biopsy specimen showed the marrow to be 80 percent cellular; 90 percent of the cells were lymphocytes. The megakaryocytes appeared normal. The granulocytic series was substantially reduced in number with a pronounced shift to the left and only rare early precursors. Erythroid maturation was normoblastic.

Cimetidine therapy was discontinued on the patient's admission, and administration of gentamicin, carbenicillin and nafcillin was begun for presumed unidentified bacteremia. Local care was given for the ulcers and topical nystatin was prescribed for oral and esophageal candidiasis. He was given granulocyte transfusions the morning after admission, and these were continued daily for the next ten days.

He defervesced during the first 48 hours after admission. After two weeks in hospital, small numbers of monocytes, followed by band forms, and then polymorphonuclear neutrophils, appeared in the peripheral blood smears, and by the middle of the third hospital week the granulocyte counts had returned to normal (Figure 1).

A bone marrow aspirate and biopsy specimen obtained on the 20th hospital day showed 80 percent cellularity. The megakaryocytes were slightly increased in number. The granulocytic series showed complete and normal maturation. The erythroid line was slightly hyperplastic with normoblastic maturation, and the myeloid to erythroid ratio was 3:1. Mature lymphocytes were increased in number, with a diffuse pattern including occasional small nodules, and comprised about 50 percent of the total cellularity.

In Vitro Studies

Tissue from the patient's marrow obtained during his recovery (hospital day 20) and from marrows of healthy volunteers were cultured in vitro in the presence of cimetidine. The marrow samples were cultured with and without the patient's serum collected at the nadir of his granulocytopenia (on admission) and with complement, to assess, respectively, both immune-mediated and direct cimetidine toxicity. When assayed for committed granulocyte-monocyte progenitor cells (operationally, colony-forming units—culture [CFU-C]),[6] the patient's marrow showed no increased sensitivity to cimetidine when compared with the control marrows, nor did the patient's serum (during acute phase) show any cimetidine-mediated suppressive effects. (Control range 40 to 130 CFU-C per 2×10^5 tested marrow cells; patient 48 CFU-C per 2×10^5 tested marrow cells. Control and patient's marrow cultures were equally suppressed by 500, 750 and 1,000 μg per ml concentrations of ci-

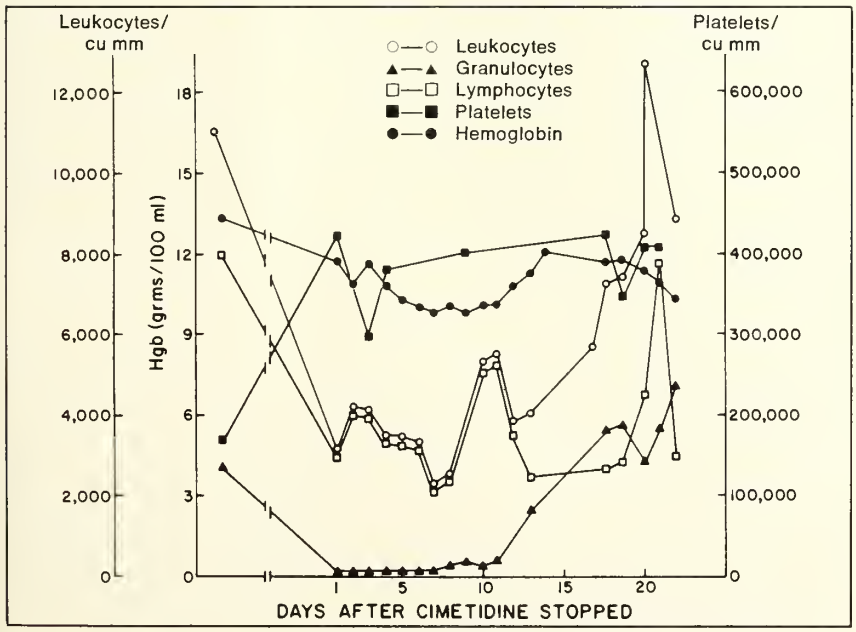

Figure 1.—Blood cell counts for patient 1. Cimetidine was stopped on the first hospital day; the first illustrated blood count was obtained three weeks earlier.

metidine, which represented approximately 100 times the usual peak therapeutic serum levels.)

CASE 2. A 57-year-old white woman with a 20-year history of peptic ulcer disease was admitted to Cedars-Sinai Medical Center in March 1979 because of oropharyngeal hemorrhagic vesicles and purpura.

Ten days before admission she experienced palpitations and took two or three quinidine tablets, which she had taken for several months a year previously. No further quinidine was taken after she visited her physician that day.

Seven days before admission, she returned to her physician because of recurrence of her typical ulcer pain. Administration of cimetidine, 300 mg orally three times a day, was prescribed and relief of her symptoms occurred within 48 hours.

During the two days before admission hemorrhagic blebs developed, first on the lips and then on the oropharyngeal mucosa and tongue. On the day of admission, she awoke with purpura over her entire body.

She stated that she had no previous history of bleeding, easy bruising, lymph node enlargement, recent upper respiratory tract infection, hepatitis, renal disease or connective tissue disorder. She had ingested no quinine-containing beverages and had no history of exposure to chemical toxins. Her most recent blood cell count, done several months earlier, included hemoglobin 11.9 grams per dl, hematocrit 36.0 percent and leukocyte count 5,400 per cu mm, with 54 percent neutrophils, 43 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils; adequate platelets were noted. Her other medications included conjugated estrogens, USP 0.625 mg taken orally 15 days per month for menopause symptoms, and acetaminophen, 325 mg taken orally several times a week for headaches.

She was afebrile on admission. On physical examination, small purpuric areas over all four extremities and confluent petechiae on her legs and ankles were noted. Hemorrhagic bullae were present on the oropharyngeal mucosa, tongue and lips. There was no enlargement of lymph nodes, liver or spleen.

On admission, laboratory data included the following: hemoglobin 15.0 grams per dl, hematocrit 43.0 percent, normal erythrocyte indices and leukocyte count 2,100 per cu mm, with 54 percent neutrophils, 43 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils; platelet count was 2,000 per cu mm. Prothrombin time, partial thromboplastin time, serum protein electrophoresis and creatinine values were within normal range. No quinidine was detected in her serum. Her serum muramidase value was normal, and Coombs, sucrose hemolysis and mononucleosis spot tests were negative. Assays for hepatitis B surface antigen, rheumatoid arthritis latex factor, antinuclear antibodies and lupus erythematosus cells were all negative.

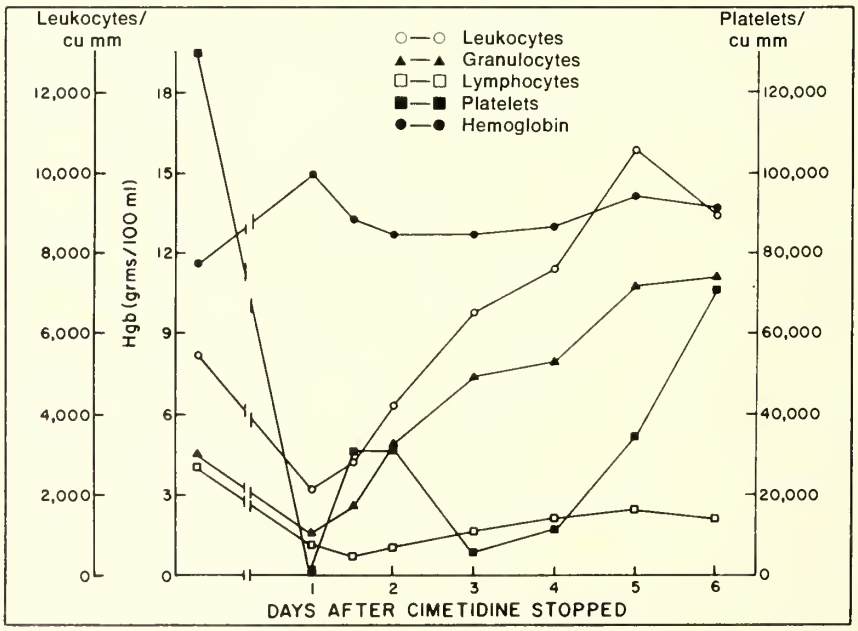

Figure 2.—Blood cell counts for patient 2. Cimetidine was stopped on the first day in hospital; the first illustrated blood cell count was obtained three months earlier.

A bone marrow aspirate and biopsy, obtained at the time of admission, showed slight hypocellularity and mild megakaryocytopenia. There was a pronounced shift to the left in the granulocytic series, with a predominance of young forms and rare fully segmented cells. Erythroid maturation was normoblastic, and the myeloid to erythroid ratio was 2:1. The lymphocytes were normal.

On admission, all medications were discontinued, and the patient was given platelet transfusions and 40 mg of methylprednisolone intravenously followed by 40 mg of prednisone orally twice a day. Antacids were administered orally for peptic ulcer disease. During the next several days, the leukocyte count returned to normal; during the next week, the platelet count returned to normal as well (Figure 2).

A bone marrow aspirate obtained 11 days after admission showed normocellular marrow with normal maturation of the granulocytic series and normal numbers of megakaryocytes. Erythroid maturation was normoblastic and the myeloid to erythroid ratio was 3:1.

In Vitro Studies

To investigate the role of drug-related antibody-mediated platelet destruction, the patient's serum, collected at the nadir of her thrombocytopenia (pretreatment, on admission), was tested in vitro in the presence of normal donor platelets and was compared with normal control serum. Using the radioactive chromium (^{51}Cr)-labeled platelet lysis method (with complement),[7] donor platelets lysed in combination with the patient's serum without the addition of quinidine or cimetidine. A positive reaction for antibodies in the absence of either drug was also obtained by the fluorescent antibody technique,[8] confirming the presence of sufficiently high serum antibody activity to prevent detection of specific drug-dependent antibodies.

Platelet antibody studies were repeated using serum collected after return of the blood counts to normal (day 11). Using the fluorescent antibody technique, recovery serum tested positive for antibody each with cimetidine (+) and quinidine (+++) (maximum positive [++++]), while serum alone tested negative.

To test for antibody-mediated as well as direct bone marrow toxicity, cimetidine and quinidine were each incubated with marrow tissue cultures, with and without the patient's serum, at the nadir of the cytopenia (pretreatment, day 1); the cultures were assayed for granulocyte-monocyte progenitor cells (CFU-C).[6] The patient's marrow showed no increased sensitivity to quinidine or cimetidine, with or without acute-phase serum and complement, when compared with control cultures from normal human marrow. (Control range 40 to 130 CFU-C per 2×10^5 tested marrow cells; patient 75 CFU-C per 2×10^5 tested marrow cells. The marrow specimens of the patient and the controls were suppressed equally at 500, 750 and 1,000 μg per ml of cimetidine, approximately 100 times the usual peak therapeutic serum levels.)

Comments

Metiamide, the first widely used histamine H_2 receptor antagonist, was effective in treatment of hypersecretory upper gastrointestinal disorders, but it was withdrawn from clinical use following reports of associated agranulocytosis.[9,10] Cimetidine, which differs from metiamide by replacement of the thiourea side chain with a cyanoguanidine moiety, did not show bone marrow suppression in animal and clinical trials,[11,12] and it has become widely used in the treatment of peptic ulcer disease and Zollinger-Ellison syndrome. Reversal of metiamide-induced bone marrow suppression and agranulocytosis after replacing metiamide with cimetidine,[9] and a report of cimetidine tolerance by a patient in whom a metiamide-related agranulocytosis had developed six months earlier,[10] have been advanced as evidence that metiamide bone marrow toxicity is unique to that compound.[13] Further, it has been suggested that the elimination of the thiourea group in cimetidine may be the reason for the lack of marrow toxicity found with metiamide.[14] In vitro, radioactive hydrogen (^3H)-labeled metiamide, like radioactive sulfur (^{35}S)-labeled thiourea, is retained by a variety of bone marrow cells, while there is no (^3H)-labeled cimetidine uptake.[15] This suggests that metiamide, with its thiourea side chain, may more easily gain *access* to the stem cell to effect its toxicity. Indeed, the actual *mechanisms* of toxicity of metiamide and cimetidine may not differ. Reports by Byron describing in vivo bone marrow experiments suggest that the action of metiamide may be histamine H_2 receptor-mediated and, thus, may be common to both drugs.[16-18] Using the mouse pluripotent stem cell (CFU-S) assay, he demonstrated that H_2 receptor-mediated stimulation of stem cell division can be blocked by both metiamide and cimetidine.

The bone marrow biopsy specimens obtained

from both of our patients at the time of acute granulocytopenia showed marrow depletion of the granulocytic series. The bone marrow tissue culture studies showed no cimetidine-mediated (antibody-mediated or direct) depression of granulocyte progenitor cell activity (CFU-C) in our patients' marrow specimens when compared with marrow specimens from normal controls. Although necessarily limited by the sensitivity of in vitro study,[19] these results showed that our patients had no unusual intrinsic sensitivity to drug-mediated bone marrow toxicity. Most consistent with our data and other reported cases of cimetidine-associated cytopenia, as suggested by Byron,[18] Freston[3] and Selker and colleagues,[25] is the possibility that cimetidine has a generalized effect on marrow stem cells that may become manifest as peripheral cytopenia when another insult has already caused preexisting progenitor cell reserve depletion. It seems likely that our patients had reduced stem cell reserves at the time of cytopenia. The first patient had leukemia and also had received the alkylating agent chlorambucil; both of these factors can reduce granulocyte precursor reserves.[20,21] The longer duration of granulocytopenia in this patient may have been related to a more severe underlying marrow derangement and also to ongoing additional marrow reserve depletion by concomitant sepsis.[22] As demonstrated by the antibody detection studies, the second patient had an ongoing destructive immune process (thrombocytopenia), which also can cause stem cell reserve depletion.[23,24] The possibility that cimetidine toxicity is related to the presence of underlying marrow injury is additionally supported by the observation of substantially more severe nadirs of granulocytopenia in six of eight patients receiving cimetidine concomitantly with carmustine (BCNU) chemotherapy for brain tumors than in patients in a large group not receiving prophylactic cimetidine.[25] Also consistent with this is a recent report describing a patient treated with methotrexate in whom reproducible cimetidine-associated severe granulocytopenia developed.[26] Indeed, nearly all of the previously reported cases of cimetidine-associated granulocytopenia have included coexisting processes that are known to reduce bone marrow reserves such as sepsis, immune diseases, renal failure or hematologic malignancies.

The cause of thrombocytopenia in case 2 is uncertain from our experiments and may be multifactorial. Because the serum collected on admission caused donor platelet lysis without added drug, it is likely that she had either antiplatelet antibodies or already formed immune complexes in the circulation during the time of the acute cytopenia. Because her serum specimens during convalescence showed both cimetidine-dependent and quinidine-dependent antibody activity, the relative roles of the two drugs cannot be well assessed. Although the possibility of primarily quinidine-related thrombocytopenia cannot be eliminated, the ten-day delay after ingestion is somewhat atypical, and the decreased, rather than increased, number of bone marrow megakaryocytes argues against typical quinidine-immune thrombocytopenia. However, these observations are consistent with a suppressive effect on bone marrow megakaryocytes by cimetidine with a concomitant immune process affecting the megakaryocyte line, which in turn causes an effect on platelet precursors essentially analogous to the situation proposed above for the granulocytic line. Further, this is consistent with two other reported cases of cimetidine-associated thrombocytopenia, in which there were additional concomitant causes of thrombocytopenia (immune thrombocytopenia associated with systemic lupus erythematosus in one and alcohol abuse in the other).[4,5,24,27]

Cimetidine, having been used by about 11 million patients, has been associated with leukopenia at an approximate rate of one per 100,000 and agranulocytosis in approximately one in three million (Unpublished data, M. L. Gifford, Director of Medical Affairs, Smith Kline & French Laboratories, Philadelphia, Dec 1980). (A summary of all reported cases of cimetidine-associated cytopenia is presented in Table 1.)

Bone marrow suppression was noted in marrow biopsy specimens in approximately 1 percent of patients with peptic ulcer disease who were taking metiamide,[12] despite the far less frequent occurrence of agranulocytosis. This supports the possibility that inapparent degrees of modulation of the pleuripotent stem cell by H_2 receptor antagonists may be more frequent than are noted clinically. Bone marrow suppression by cimetidine may only become significant enough to alter the circulating cell populations in patients who already have compromised or stressed stem cell reserves, as was likely in the two cases reported here. This possibility reinforces the need for restricting the use of this drug to established indications, and particularly suggests the need for monitoring hematologic values in patients having diseases or

TABLE 1.—*Summary of 25 Cases of Cimetidine-Associated Cytopenia*

Authors and Ref. No.	Patient's Age	Peripheral Blood Count at Nadir (10^3/cu mm) Leukocytes	Granulocytes	Platelets	Clinical Problem	Possible Marrow-Suppressing Condition	Other Medications
		(First exposure)					
Carloss et al[26]	67	2.2	0.022	217	Pyloric ulcer, psoriasis	Methotrexate	Furosemide, spironolactone, retinoic acid
		(Re-exposure)					
		2.4	0.048	*			None during reexposure
Corbett & Holdsworth[28]	44	2.7	1.80	*	Duodenal ulcer, urinary tract infection	? Sepsis	Sulfamethoxazole-trimethoprim
Chang & Morrison[29]	66	0.30	0.0	186	Gastric ulcers	*Klebsiella* and streptococcal sepsis	Dioctyl calcium sulfosuccinate
Craven & Whittington[30]	28	2.2	0.022	205	Duodenal ulcer	None noted	Metoclopramide, acetaminophen, penicillin V, poldaine methylsulfate
Idvall[5]	75	*	*	19	Gastric ulcer	None noted	"None suspicious for cytopenia"
	57	*	*	20	History of peptic ulcer, liver failure	Alcohol abuse, liver failure	"None suspicious for cytopenia"
Isaacs[31]	43	6.6	4.01	6	Gastric ulcer	Sarcoidosis	Prednisolone
James & Prout[2]	41	3.0	*	30	Hematemesis	Proteus sepsis	Gentamicin, ampicillin
Johnson et al[32]	39	2.8	1.6	100	Duodenal ulcer, *Salmonella* gastroenteritis	? Sepsis	*
Klotz & Kay[33]	62	3.1	1.86	57	Antral gastritis, arthritis	Autoimmune thrombocytopenia	Hydrochlorothiazide, propranolol, levothyroxine, prednisone
Lopez-Luque et al[1]	29	2.3	1.41	*	Duodenal ulcer, hypertension, fever	None noted	Tranexamic acid, clorazepate
McDaniel & Stein[4]	77	*	*	24	Chronic obstructive lung disease, cecal carcinoma, history of ulcer disease	Carcinoma	Corticosteroids
Posnett et al[34]	43	1.7	0.62	120	Gastric ulcer	Lymphoma	Dioctyl calcium sulfosuccinate
Rate et al[35]	53	3.1	1.86	57	Gastritis, crytogenic cirrhosis	Hemolytic anemia	*
Sazie & Jaffe[36]	17	1.4	0.12	"Normal"	Subdural hematoma, staphylococcal bacteremia	Phenytoin	Phenytoin, tobramycin, dexamethasone
Selker et al[25]†	(six patients)	<0.5	*	<8	Brain tumors (GI prophylaxis: see text)	Carmustine	*
Ufberg et al[14]	62	1.3	0.026	77	Duodenal ulcer, hypertension, renal failure	Uremia	Digoxin, clonidine
Wallin et al[37]	78	2.4	0.0	240	Upper GI bleeding, cirrhosis	Phenytoin, alcohol abuse	Phenytoin (for 20 years), spironolactone, tobramycin, cefazolin
Present cases	78	3.2	0.032	420	Presumed ulcer disease	Chronic lymphocytic leukemia; prior chlorambucil treatment	Prednisone
	57	2.1	1.10	2	Duodenal ulcer	Immune thrombocytopenia	Estrogens, acetominophen, prior quinidine

GI = gastrointestinal

*Not specified

†Data cover six patients in study. All six had <0.5 leukocytes, granulocytes not specified and <8 platelets (10^3/cu mm), brain tumors and carmustine therapy.

receiving treatments associated with depressed bone marrow reserves.

Summary

Cimetidine-associated granulocytopenia was observed in two patients, one with concomitant thrombocytopenia and both with probable underlying bone marrow reserve compromise. In vitro bone marrow cultures from these patients did not differ from control marrows in sensitivity to cimetidine when assayed for granulocyte-monocyte progenitor cells (CFU-C). Platelet antibody studies showed evidence for drug-mediated thrombocytopenia in one patient, but there was evidence also for primary bone marrow megakaryocyte suppression. The data from these patients suggest that there may be a generalized bone marrow suppressive effect of cimetidine, which becomes manifest as peripheral cytopenia only when a significant preexisting insult has caused marrow stem cell reserve depletion. This hypothesis is discussed in light of other experimental data and other reported cases of cimetidine-associated cytopenia.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Adoption and the Rights of Biological Parents

TO THE EDITOR: The article "Adoption: Pediatric, Legislative and Social Issues"[1] brings to mind a question that is ignored by this and other similar articles: What about the right of the biological parents to remain anonymous? If an adopted child has an interest in his biological parentage does he or she have the privilege to violate that right of anonymity?

Also is the term *biological parent* a valid one? By definition a parent is one that begets or brings forth offspring.[2] However, in the context of a human life and in view of the present and near future technology of conception and birth, begetting is almost trivial.

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2. Webster's New Collegiate Dictionary. 1980 Ed. Springfield, MA, G. & C. Merriam Co, p 826

Autologous Blood Products

TO THE EDITOR: Coagulum pyelolithotomy is an accepted urological procedure which can be utilized for the removal of renal calculi when preoperative assessment suggests it may be difficult to remove calculi by conventional surgical methods. The coagulum is formed at the time of the operation by mixing appropriate amounts of calcium chloride, thrombin and cryoprecipitate.

Reduced risk of hepatitis transmission and safety from cross-matching error are major advantages for patients who receive autologous blood products. Recently we were able to extend this advantage by providing autologous cryoprecipitate along with autologous red blood cells for a patient undergoing elective coagulum pyelolithotomy.

To provide adequate amounts of plasma for cryoprecipitate production, plasmapheresis was carried out. Autologous red cells were obtained well in advance of the surgical procedure. These products were then transferred to the operating room from the blood bank at the time of the operation. The procedure was carried out without incident.

There are added expenses associated with the use of autologous blood products. However, one must weigh the advantages of added safety for the patient against such added costs. Where plasmapheresis support is available the use of autologous blood and blood products should be considered as an alternative approach for patients who are to undergo coagulum pyelolithotomy.

LACEY HICKS, MT(ASCP)SBB
LEE B. HARBACH, MD
RALPH P. GEORGE, MD
San Diego Blood Bank
San Diego

Molten Metal Burns on the Feet

TO THE EDITOR: In the article "Molten Metal Burns"[1] in the July issue the authors call attention to a body area that is indeed "sneaky" when burned with molten metal, and that is the foot. Most of these burns on the feet result from the metal actually burning through the tongue of a work shoe. A significant percentage happen when metal runs inside the top of the boot and comes to rest on the exterior surface of the foot on the heel. In either case, the shin and subcutaneous tissue is relatively thin and a deep burn is a common result. Part of the problem includes the fact it takes some time to get the shoe off.

In the aluminum industry, another facet of the burn is that caustic chemicals add an additional chemical burn if the source of the metal is a smelting pot. Because of the caustic, the immediate treatment of the burn should be immersion in water for 20 to 30 minutes.

In a smelter or foundry, these burns are fairly common. The total of 16 cases in a seven-year period that the authors mention does not seem excessive for a burn center. In my experience, most of these smaller burns can be handled on an outpatient basis. The mainstay of treatment is the availability of a nurse who can see the patient

twice a day. At each visit, the wound should be soaked in warm, soapy water before a clean dressing and some agent such as silver sulfadiazine (Silvadene) is applied. If any sign of cellulitis or gross infection appears, the patient should immediately be referred for definitive care.

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REFERENCE

1. Kahn, MA, McCrady-Kahn VL: Molten metal burns (Information). West J Med 135:78-80, Jul 1981

The Halsted Mastectomy

To the Editor: I am disturbed by the article "The Halsted Mastectomy: Present Illness and Past History."[1] The aggressive feminist "macha" can of course write as she wishes—it is easy to brush aside the milieu of a century ago and to select those statements or opinions that best fit one's current literary endeavor. Rational thinking can be replaced by cuteness. Halsted was a leader of his time, and were he here today he would indeed be a leader. It is most unlikely that he would advocate the same surgery now as then. Rather, he would be thrilled and challenged by the new opportunities of the past two generations.

The only real complaint about the article is the wisdom of the editor in accepting it for publication.

GORDON T. BOWEN, MD
Lynwood, California

REFERENCE

1. Bland CS: The Halsted mastectomy: Present illness and past history (Special Article). West J Med 134:549-555, Jun 1981

* * *

To the Editor: The article "The Halsted Mastectomy: Present Illness and Past History" by Cordelia Shaw Bland was most entertaining. Although it is true that indications for a classical radical (Halsted) mastectomy are few at present, we take exception to most of her conclusions.

First, radical mastectomy was designed to remove the breast in continuity with its lymphatic drainage (including the transpectoralis lymphatic route), a principle of surgical oncology that had yielded higher cure rates in other organs, and not merely to separate surgeons from general practitioners as suggested by the author. It was accepted not because of economic or nationalistic reasons but because of the markedly lower incidence of local recurrence following this operation (Table 1).[1] While it is true that there is no correlation between survival and local recurrence, and in fact locally recurrent tumor is rarely the immediate cause of death among patients with breast cancer, this problem should not be underestimated. Ulcerated malodorous lesions of the chest wall are certainly a source of great distress to any patient with cancer and prevention of local recurrence is definitely one of the main goals of any treatment modality. When radical mastectomy was introduced, the average patient presented with advanced local disease and relatively extensive procedures were needed to achieve local control of the lesion. Fortunately this is no longer the case.

TABLE 1.—*Local Recurrence After Halsted's Radical Mastectomy Versus Recurrence After Lesser Procedures by Well-Known Surgeons of Late 19th Century**

Operator	*Time*	*No. of Cases*	*Local Recurrence (percent)*
Bergmann	1882-1887	114	51-60
Billroth	1867-1876	170	82
Czerny	1877-1886	102	62
Fischer	1871-1878	147	75
Gussenbauer	1878-1886	151	64
Konig	1875-1885	152	58-62
Kuster	1871-1885	228	59.6
Lucke	1881-1890	110	66
Volkmann	1874-1878	131	60
Halsted	1889-1894	50	6

*Adapted from Degenshein.[1]

Second, it is not true that radical mastectomy (or modified radical mastectomy) "rules out plastic surgery for a reconstructed breast," as a number of reconstruction modalities with good cosmetic results are available after these operations.[2,3]

Third, studies of the natural history of the disease suggest that carcinoma of the breast probably encompasses a heterogeneous group of diseases with variable time courses, but not necessarily that carcinoma of the breast is systemic in all patients from the beginning.[4] If the latter were true, and if local control were not important, then all screening programs for early detection would be a waste of time since early diagnosis and treatment would not influence the prognosis. This, of course, is not the case and even those who believe breast cancer is a systemic disease from the start advocate early treatment for patients with minimal breast lesions (positive mammograms, with negative physical examination of the breast and nodes).

Fourth, it is inaccurate to state that "limited excision (lumpectomy) followed by primary high-dosage irradiation is now considered the major alternative to radical mastectomy." Preliminary data suggest that segmental mastectomy plus

radiotherapy gives good results in patients with stage I,[5] but there is still controversy regarding the best treatment modality for breast cancer.

We believe that modified radical mastectomy is, at present, the procedure of choice for *most* patients with potentially curable carcinoma of the breast. This modality appears to cure the disease in patients in whom cancer is localized (about 20 percent of patients with breast cancer) and at the same time provides valuable staging information. The latter can be used to establish prognosis since the number of nodes involved is the single factor most predictive of 10-year and 20-year survival,[6] and most important the information obtained from the pathologic examination of the axillary lymph nodes is vital to ascertain the need for adjuvant therapy.

Finally, we believe it is unfair to imply or state that Halsted did not practice what he preached, that his operation was designed only to promote the economics of surgery, that he charged exhorbitant fees and that he avoided patients at all times. It is unjust to minimize his contributions in the field of asepsis, one of the greatest advances in surgery, pretending they represented only a romantic event. If it was important for the author to describe in detail Halsted's drug addiction and character problems it might also have been fair to point out that it was William S. Halsted's prodigious mind that laid the structure for the surgical residencies, the system used in training surgeons throughout the world today.

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6. Fisher B, Slack NH: Number of involved nodes examined and the prognosis of breast carcinoma. Surg Gynecol Obstet 131: 79-88, 1970

* * *

TO THE EDITOR: I wish to commend you on your publication of Cordelia Shaw Bland's article on the Halsted mastectomy in your June issue. I felt a little ill inside when I read it.

It has always amazed me how much we physicians are influenced in how we practice medicine by those who often have so little direct contact with the kind of medicine *we* see on a daily basis. I can remember 25 years ago being told "pure gospel" by physicians who had never, and would never, be directly involved in the day-to-day caring for people.

As physicians, we are privileged to have the most intimate look at the best and worst of the human condition, and, if we seriously think or care at all about what we spend most of our time doing, I rather think our judgment will be quite good most of the time. But can we embark on what might turn out to be a better treatment when we are constrained by our attorney friends, and in fact our peers, to limit our treatments to the so-called community standard?

NORMAN C. HEADLEY, MD
Cameron Park, California

* * *

TO THE EDITOR: I look forward each month to THE WESTERN JOURNAL OF MEDICINE as a source of information regarding medical developments in the western states.

I write you now, however, to register a firm voice of displeasure regarding the publication of the article by Cordelia S. Bland in the June issue.

The article is filled with innuendo and extrapolation.

There is lack of logic, specious reasoning and repeated assumption that play no role in a medical journal. Reference to nonfactual material and to authors with an acknowledged bias is not appropriate.

Publishing the article represents an extremely poor editorial philosophy. The article falls well below the standard I expect from you.

SONNY P. COBBLE, MD
Los Angeles

* * *

TO THE EDITOR: Congratulations on the great article by Cordelia S. Bland. I thoroughly enjoyed it. It was written objectively and scientifically. THE WESTERN JOURNAL OF MEDICINE showed very good taste in accepting it. And, I congratulate the author on a job well done. Keep up the good work.

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* * *

TO THE EDITOR: The article on the Halsted mastectomy in the June issue has proved a delight to

me to the extent that I must pass along my appreciation.

The scholarship was most enjoyable, certainly, but the insight into the human and sometimes less than normally human attributes of physicians, however elevated in professional stature, was even more intriguing.

The fact that I have agreed with the article's tenets for some decades, of course, creates an even greater sense of gratification in reading the excellent prose.

Congratulations to the author on her literary and intellectual efforts.

ROBERT D. DUNBAR, MD
Modesto, California

Psychiatric Symptoms of Neurosyphilis

To the Editor: This is regarding the article entitled "The Great Imitator, Syphilis" in the May 1981 issue.[1] All in all it was an excellent article, well written and of course very timely.

I wonder if Dr. Fitzgerald would be willing to comment a little on aspects of tertiary syphilis that we in psychiatry have to bear in mind. I believe it is a point not covered in the article.

Treatment of incidental infections with penicillin or other antibiotics will often convert the peripheral blood VDRL. The physician then, in getting either routine studies or serologic studies in suspected cases, may be lulled into a false sense of security. After the treatment of the incidental infection and the conversion to seronegative peripheral blood, is not the disease then permitted to continue, often not surfacing until the tertiary stage? Would Dr. Fitzgerald perhaps have some helpful hints on how to make a diagnosis of paresis in such a case?

Recently I became sensitized to such a case. The patient was a 59-year-old Puerto Rican man of Carribe extraction. Clinically he presented as a paretic. The VDRL peripherally was negative and it was only when clinical evidence forced me to do a lumbar puncture and an FTA-ABS (fluorescent treponemal antibody absorption test), which turned out positive, that we were able to make a diagnosis and initiate treatment.

With the ever-increasing use of antibiotics to treat minor illnesses and with the increasing incidence of venereal disease in general and syphilis in particular, is not this a danger that we are overlooking?

J. M. STUBBLEBINE, MD
Greenbrae, California

REFERENCE

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* * *

The Author Replies

To the Editor: Dr. Stubblebine raises a most important point. Syphilis at one time was said to account for 10 percent to 20 percent of admissions to state mental hospitals.[1] Though this is no longer the case, syphilis must still be considered in the differential diagnosis of almost every mental disease. As Dr. Stubblebine implies, antibiotic therapy may have altered the classical clinical patterns of neurosyphilis.[2] Though it is generally accepted that antibiotic therapy which leads to reversion to seronegativity in early syphilis constitutes a "cure,"[3-5] two unresolved issues confound absolute surety on this point. First, of course, is that spontaneous reversion to seronegativity is common even in *untreated* lues, and a quarter to a half of all patients with late syphilis will have a negative serum VDRL.[2,6] In one study, only 48.5 percent of neurosyphilitic patients—some of whom gave a history of previous therapy for syphilis—had reactive serologic tests for syphilis.[2] The second issue to be considered touches upon the data which suggest the persistence of spirochetes in central nervous system (CNS) tissue in spite of putatively adequate penicillin therapy and negative serum VDRL.[6]

It is best to rely, as did Dr. Stubblebine, on clinical clues. Psychiatrists might well be the first physicians consulted by the victims of neurosyphilis. Meningovascular syphilis may simulate psychoneurosis,[1] as the rare gummatous mass in the CNS can look like a brain tumor and induce personality changes. In a study of more than 200 patients with CNS lues in the penicillin era, about 9 percent had "organic brain syndrome," 5 percent depression, 3 percent mania and 2 percent other personality changes.[2]

The onset of the psychiatric symptoms of general paresis can be insidious, first noticed by family and friends rather than the patient: loss of ambition at work, memory lapses, irritability and a decline in attention to personal affairs. Later, patients may present with mental changes simulating schizophrenia, euphoric mania, paranoia, toxic psychoses or presenile dementias. The last is most common, with depression, confusion and severe impairment of memory and judgment. In the last stages of the disease, occurring generally within five years of the onset of symptoms, almost

all patients with general paresis are demented, often with periodic convulsions and progressive vegetative degeneration until they die.

Because syphilis is pleomorphic in its presentation, unexplained psychiatric disease should raise the suspicion of lues. Results of careful neurologic examination, especially in the early stages of the disease, may be entirely normal even in the face of pronounced mental changes.[7] The serum FTA-ABS is positive in 95 percent or more of all patients with general paresis.[6] Lumbar puncture may show a positive VDRL, although only 57 percent of patients with neurosyphilis in one series had CSF serology positive.[2] A positive serum FTA-ABS, with CSF mononuclear pleocytosis or an elevated protein value (or both) confirm the diagnosis for all practical purposes and should lead to appropriate therapy.

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Another Method of Water Purification for Travelers

To THE EDITOR: The article by Zemlyn, Wilson and Hellweg[1] on iodine for water purification in the August 1981 issue discussed crystalline iodine and organic iodine tablets, tetraglycine hydroperiodide, for use by backpackers for purification of drinking water. They recommended the latter.

The authors' point may well be valid, but there appears to be a much better method than either of those discussed. Povidone-iodine (Betadine) 10 percent solution is stable, safe and packaged in several sizes, including a ½ oz plastic squeeze bottle. The latter is very convenient for travelers but is not available in most pharmacies, undoubtedly because of insufficient demand. Two or three drops per glass or eight to ten drops per liter provides 3 to 4 ppm, which is sufficient to kill coliform bacteria in one or two minutes. Time required for killing viruses and *Giardia* and *Entamoeba* cysts is less clear, but may be as long as 30 minutes in very cold water; less at room temperature. The taste is quite tolerable.

Recently I contacted the manufacturer, Purdue Frederick, and learned that almost no inquiries have been received in the United States about povidone-iodine's use for drinking water purification, but that it is included for this purpose in emergency military kits in several other countries. An additional advantage, of course, is its value as a wound disinfectant and for the treatment of the various sores and superficial fungal infections so common to travelers.

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REFERENCE

1. Zemlyn S, Wilson WW, Hellweg PA: A caution on iodine water purification (Information). West J Med 135:166-167, Aug 1981

Correction: Formula to Calculate Serum Osmolality

IN THE AUGUST Medical Staff Conference, "Acute Methanol Poisoning," the formula for calculating serum osmolality was printed incorrectly on page 125. It should read as follows:

$$2 \times Na + \frac{BS}{18} + \frac{BUN}{28} = 285 \pm 4.2 \text{ mOsm/kg } H_2O.$$

Na = serum sodium concentration, mEq per liter
BS = blood sugar concentration, mg per dl
BUN = blood urea nitrogen concentration, mg per dl

Refer to: Bruce RA, Hossack KF, Belanger L, et al: A computer terminal program to evaluate cardiovascular functional limits and estimate coronary event risks (Health Care Delivery). West J Med 135:342-350, Oct 1981

A Computer Terminal Program to Evaluate Cardiovascular Functional Limits and Estimate Coronary Event Risks

ROBERT A. BRUCE, MD; KENNETH F. HOSSACK, MD; LAURENT BELANGER, MD; TIMOTHY A. DeROUEN, PhD; JOHN S. SOBOLEWSKI, PhD; VERONA HOFER, BS, *and* TED HOLZMAN, BS, *Seattle*

A system of computer terminals was set up in a group of office practices, industrial medical departments and hospitals and connected to a central computer. This service provides a means of analyzing treadmill exercise results, which are displayed graphically on the computer printout. The system also provides estimates of probabilities of primary or secondary coronary heart disease events developing based on the exercise responses.

In 1971 the Seattle Heart Watch (SHW) study[1] was begun. This was a prospective community practice study to determine antecedents of acute myocardial infarction and sudden cardiac death. An exercise testing unit was used to study the feasibility of symptom-limited maximal exercise in routine clinical practice—quantifying functional aerobic capacity, noninvasively defining mechanisms of cardiovascular impairment[2] and defining changes with serial testing.[3] The exercise protocol used and the physiological significance of the exercise responses have been presented elsewhere.[4] In all, 50 physicians from 15 centers collected clinical data concerning patients and their responses to symptom-limited maximal exercise on standardized forms. These data were mailed to the University of Washington where they were coded and stored on computer discs for subsequent analysis. During the four-year study, information on 9,212 persons was collected.

Follow-up surveillance for the occurrence of morbidity and mortality from coronary heart disease (CHD) was obtained by questionnaires mailed twice a year to patients with coronary heart disease and once a year to healthy persons. Subsequent analysis enabled characterization of subgroups of coronary patients with increased risk of sudden cardiac death[5] and patients in whom aortocoronary vein bypass grafting appeared to improve survival.[6] Subgroups of apparently normal persons[7] and hypertensive patients[8] with increased

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This study was supported by research contract and grant MB 00184 from The Bureau of Manpower, Health Resources Administration, DHEW, and HL 18805 from the National Heart, Lung, and Blood Institute, USPHS, DHEW, and the John L. Locke Jr Computer Center.

Dr. Hossack was a recipient of a Poncin Scholarship from the Seattle-First National Bank, and Dr. Belanger a recipient of a John L. McLaughlin Scholarship.

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ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
FAI = functional aerobic impairment
HRI = heart rate impairment
LVI = left ventricular impairment
PCI = peripheral circulatory impairment
PRP = product of heart rate and systolic blood pressure
SHW = Seattle Heart Watch (study)
$\dot{V}O_2$ max = maximal oxygen uptake

risk of primary coronary heart disease events were also identified.

The initial experience with the data collection process identified a need for rapid collection and analysis of the exercise responses. Such analysis was aimed at helping physicians in their interpretation of data for use in patient management. When enrollment in the SHW registry ceased in 1975, an interactive computer system supporting multiple users was established under a different grant mechanism. Since then physicians in nine testing sites have reported reponses on more than 14,000 exercise tests.

The purpose of this paper is to describe the computer system (Terminal Network Registry). The physiological implications of the exercise test are reviewed and changes illustrated with examples of computer printouts. Finally, examples of risk prediction based on exercise responses and prior Seattle Heart Watch experience are provided.

Computer System and Data Collection

The present system consists of nine computer terminals (Texas Instrument, Silent 700) with audio couplers linked by telephone line to the University of Washington's Locke Computer Center. The system serves two teaching hospitals, three private hospital-clinics, two separate laboratories of a large aerospace industrial medical department and two cardiac rehabilitation programs (Figure 1).

Each person tested gives informed consent for exercise testing, data storage and subsequent follow-up. The data are collected on standardized work sheets (see Figure 2). When the test is completed and the supervising physician has checked the data, the information is entered into the computer terminal. The computer then provides on immediate printout summarizing the findings of the test with the physiological interpretation, and, where appropriate, the relevant annual probabilities of coronary heart disease

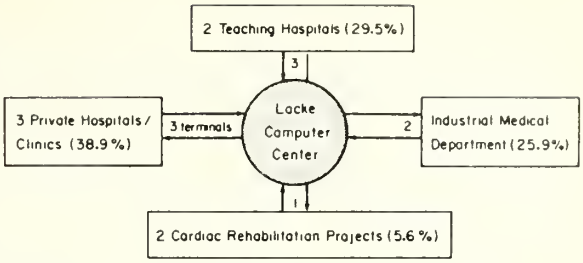

Figure 1.—Site distribution of the 2,936 tests entered in the Terminal Network Registry in 1978.

TABLE 1.—*Bruce Protocol for a Multistage Treadmill Test*

	Speed (MPH)	*Grade (Percent)*	*Oxygen Uptake ml×Min⁻¹×Kg⁻¹ (3rd Minute of Each Stage)*	
			Men	*Women*
Stage I	1.7	10	17.2	16.3
Stage II	2.5	12	26.0	24.5
Stage III	3.4	14	34.8	32.7
Stage IV	4.2	16	43.6	40.9
Stage V	5.0	18	52.4	49.6

events based on prior follow-up surveillance of the Seattle Heart Watch experience and the individual exercise test responses. Average time for data entry and computer printout is about ten minutes; the cost for this computer processing service is approximately $2 per patient.

Exercise Protocol and Its Clinical and Physiological Significance

The Bruce protocol[4] for a multistage treadmill test uses three-minute increments of graded exercise (Table 1). Previous studies showed that maximal oxygen uptake ($\dot{V}O_2$ max), weight-adjusted ($\dot{V}O_2$ max, ml/[kg×min]) could be estimated from duration of exercise in seconds from the commencement of stage I provided the person does not support his or her bodyweight with the upper limbs.[9] The regression equations for men and women, respectively, are as follows:

$$\dot{V}O_2 \text{ max} = 0.56 \text{ (duration in seconds)} + 3.99.$$
$$\dot{V}O_2 \text{ max} = 0.56 \text{ (duration in seconds)} + 1.06.^{9}$$

Reproducibility of these measurements has been documented.[9] If the resting aerobic requirement. while the person rests sitting upright, is assumed to be 4 ml/(kg×min), then the ratio of $\dot{V}O_2$ max to this resting value provides a simple measure of aerobic capacity in mets (unit equaling 50 kcal per sq meter of body surface per hour) or multiples of the resting oxygen requirement.

The importance of maximal oxygen uptake as

1. Site No
2. Accession No
3. Name
4. Date
5. Informed Consent Signed
6. Height
7. Weight
B. Sex
9. Age
10. Status
11. Smoking Habits
12. Number of Family Members with CHD
13. Cholesterol
14. Evidence for Heart Disease
    1. Inapparent
    2. Possible

    0. Healthy
    1. Hypertension
    2. Prior MI
    3. Angina pectoris
    4. PMI & AP
    5. HT, PMI & AP
    6. HT & PMI
    7. HT & AP
    8. Prior cardiac arrest
    9. Other_____
16. Major Recent Therapy
    1. None
    2. Medical (for_____)
    3. Surgical(SVG)
    4. Surgical(Other)
    5. Physical training
    6. Psychotherapy
    7. Resuscitation
    B. Unknown
    9. Other_____

16b Started (date)

17. Beta-blocker? Yes No

1B. 3 drugs & their dosages

19. This test is
    1. Symtom-limited maximal exercise test
    2. Low-level exercise test

19b This test is
    1. Initial
    2. Follow-up without clinical change
    3. Follow-up with clinical improvement
    4. Follow-up with clinical deterioration
    5. Follow-up with variable clinical status
    6. Other

20-25.

26. Rhythm
27. Leaning on Handrail
2B. Duration from Stage I
29. Chest Discomfort
    1. None
    2. Localized
    3. With radiation
    4. Persisting ≥ 3 min
    5. Persisting ≥ 6 min
    6. Relieved by carotid sinus pressure
    7. Relieved by NTG
    8. Relieved by oxygen
    9. Other_____
30. Complications of Testing
    1. None
    2. Poorly motivated
    3. Gait disorder
    4. Stopped due to 3 or more VPC's
    5. Stopped by onset of ataxic gait
    6. Cardiac arrest, defibrillated
    7. Cardiac arrest, not resuscitated
    8. Stopped by MD because of hypotension
    9. Equipment failure
    10. Other_____
31. ST Displacement after Exercise
    1. None
    2. Upsloping depression ≥1mm for .06 second
    3. Horiz or downsloping depression ≥1mm for .06 sec
    4. Upsloping to horiz or
    5. Accent dig. effect
    6. Elevation ≥ 0.5mm
    7. Other_____

31b ST Persistance
    1. ≤ 1 min
    2. ≥ 1 min
    3. ≥ 3 min
    4. ≥ 5 min
    5. ≥ 7 min

32. Arrhythmia
    0. None
    1. Single PC
    2. 2 or more PC/min
    3. Ventricular in origin
    4. Multifocal
    5. Atrial fib or flutter
    6. Paroxysmal tachycardia
    7. Ventricular tachycardia
    B. Ventricular fibrillation
    9. Other_____
33. Heart Dimensions
    0. Reduced
    1. Normal
    2. Enlarged Slightly
    3. Enlarged Moderately
    4. Enlarged Markedly
    5. Other_____
34. Was Resting ECG Abnormal?
    Yes No

35. Supraventricular Arrhythmia
    0. None
    1. Sinus tachycardia
    2. PACs >10/min
    3. Atrial tachycardia
    4. Atrial flutter
    5. Atrial fibrillation
    6. Nodal tachycardia
    7. Left atrial enlargement
    8. Other_____
36. Ventricular Arrhythmia
    0. None
    1. PVCs <5/min
    2. PVCs >5/min
    3. Multifocal PVCs
    4. Ventricular tachycardia
    5. Other
37. QRS Abnormality
    0. None
    1. LVH
    2. LAD >-30
    3. RAD <+90
    4. DMI
    5. AMI
    6. Other
38. ST-T Abnormality
    0. None
    1. ST elevation >0.5mm
    2. ST depression >0.5mm
    3. ST depression >1.0mm
    4. LVI
    5. Digitalis effect
    6. Other
39. Conduction Abnormalities
    0. None
    1. Primary AV block
    2. Secondary AV block
    3. Tertiary AV block
    4. LBBB
    5. RBBB
    6. Intraventricular block
    7. Other
40. Symptoms and Signs with Exercise Normal
    Fatigue
    Weakness
    Sweating after 6 min exercise
    Accented sounds
    Increased P voltage
    Other
41. Borderline
    Anxiety
    Dyspnea
    Dizziness
    Nausea
    Pallor
    Accented murmurs
    Tic-tac sounds
    Beat-to-beat abberation
    2° AV, Wenckebach
    RBBB
    LAHB
    Other
42. Abnormal
    Claudication
    Sweating within 4 min of exercise
    Fainting or syncope
    Atrial gallop (S4)
    Vent Gallop (S3)
    Pulmonary congestion
    Pulsating jugular veins of tricuspid regurgitation
    Cyanosis
    Bigeminy, Coupling, R-on-T
    Mobitz type II block
    3° AV block
    RBBB & LAHB
    IVCD LBBB
    Other

STAGE S.L.M.E.T.	mph-grade L.L.E.T.	Pressure Syst.	Pressure Diast.	Heart Rate	STAGE (mph-grade)	Pressure Syst.	Pressure Diast.	Heart Rate
REST	REST				V (5.0 -18%)			
½ (1.7 - 5%)					FINAL MINUTE			
I (1.7 -10%)	I (1.2 -0%)				0 Recovery			
II (2.5 -12%)	II (1.2 -3%)				1 minute Rec.			
III (3.4 -14%)	III (1.2 -6%)				3 minute Rec.			
IV (4.2 -16%)	IV (1.7 -6%)				5 minute Rec.			

Figure 2.—Standardized Work Sheets for collection of data to be entered into the Terminal Network Registry.

a measure of cardiovascular function relates to maximal cardiac output. Cardiac output equals $\dot{V}O_2$ max divided by the arterio-mixed venous oxygen difference (Fick principle). In the absence of anemia or hypoxemia, it is unusual for arterial-mixed venous oxygen difference to be reduced in cardiac patients; therefore, reductions in $\dot{V}O_2$ max closely reflect reductions in maximal cardiac output.[10] Normally, $\dot{V}O_2$ max is greater in men than in women, is higher in physically active than in sedentary persons and declines inexorably with age; average normal values adjusted for these determinations can be predicted.[9] Functional aerobic impairment (FAI) is a percentage measure of the reduction in $\dot{V}O_2$ max adjusted for age, sex and activity status:

$$\text{FAI} = \frac{(\text{age-predicted } \dot{V}O_2 \text{ max} - \text{estimated } \dot{V}O_2 \text{ max})\ 100}{\text{age-predicted } \dot{V}O_2 \text{ max}}.$$

Nomograms for a rapid estimation of FAI from duration of symptom-limited maximal exercise by the Bruce protocol have been provided.[9]

During exercise, heart rate and blood pressure are recorded at each minute. The product of heart rate and systolic blood pressure ($\text{PRP} \times 10^{-2}$) at maximal exercise is an index of maximal myocardial oxygen consumption.[11]

In a similar fashion to FAI, heart rate impairment (HRI) and left ventricular impairment (LVI) are calculated in terms of age-adjusted and sex-adjusted normal values[2]:

$$\text{HRI} = \frac{(\text{age-predicted heart rate max} - \text{observed heart rate max})\ 100}{\text{age-predicted heart rate max}}$$

for healthy men heart rate max $= 210 - 0.662$ (years of age).

$$\text{LVI} = \frac{(\text{age-predicted PRP} \times 10^{-2} \text{ max} - \text{observed PRP} \times 10^{-2} \text{ max})\ 100}{\text{age-predicted PRP} \times 10^{-2} \text{ max}}$$

for healthy men PRP max $= 364 - 0.58$ (years of age).

The difference between FAI and LVI is designated the peripheral circulatory impairment (PCI). Thus, in a person who has a healthy heart but poor physical conditioning, this value will be large, whereas in the cardiac patient who undergoes physical training, this value is decreased as a result of peripheral conditioning.

Equivalent functional age is defined as the age equal to a healthy person matched for gender and activity status who would have a zero FAI for the estimated $\dot{V}O_2$ max of the person being tested. When positive values of FAI are found, then functional age exceeds the chronological age; when negative values are obtained, the functional age is less than the chronological age. Estimation of functional age provides a more readily understood reference standard of the whole body-integrated functional capacity.

The computer program analyzes the results of the exercise test using these measurements. The values are adjusted for gender, age, weight and activity status, and are *schematically* represented as functional aerobic capacity/impairment, left ventricular capacity/impairment, heart rate capacity/impairment and peripheral capacity/impairment for easier appraisal of functional limits of global cardiovascular physiology (see Figure 2).

Events in coronary heart disease include both morbidity and mortality. Morbidity is defined by admission to hospital for diagnosis, treatment, or both, of CHD. In healthy or hypertensive persons without prior clinical manifestations, the first of such occurrences represents a primary event. Previously recognized clinical manifestations of CHD are defined as follows: typical angina pectoris with exertion or emotion, relieved by rest or nitroglycerin; typical myocardial infarction with appropriate electrocardiographic and enzyme changes, or sudden cardiac arrest with resuscitation by ventricular defibrillation. When such patients have another clinical manifestation of cardiac morbidity or mortality, it is designated as a secondary event.

Prediction of Risk Probabilities

These predictions are based on the follow-up data of the SHW participants. In each case, risk is expressed as a probability of developing subsequent primary or secondary coronary heart disease events within one year.

Primary Coronary Heart Disease Events in Apparently Healthy Men

Analysis of 2,365 healthy men showed that in 47 (2 percent) coronary events had occurred during a mean follow-up of 5.6 ± 1.4 years.[7] A count indicating the presence of conventional risk factors (positive family history of heart disease, smoking, serum cholesterol level greater than 250 mg per dl or resting systolic blood pressure greater than 140 mm of mercury) was found to be associated with increased rates of CHD events. Univariate analysis showed that four exercise variables were important. They were (1) chest pain during exercise, (2) duration of exercise less than six minutes from the start of stage I, (3) failure to attain 90 percent of age-predicted maximal heart rate (HRI greater than 10 percent) and (4) ische-

```
        MALE     AGE: 46        ACTIVITY STATUS: SEDENTARY
        HEIGHT: 180 CM.         WEIGHT:    83 KGMS.

        RISK FACTORS--
       *SMOKING HABITS:  1 PACK CIGARETTES DAILY
       *POSITIVE FAMILY HISTORY OF CHD (# OF PARENTS/SIBLINGS): 2
       *CHOLESTEROL: 320 MGM% (> 95TH PERCENTILE )
        HYPERTENSION: NO

CARDIOVASCULAR DISEASE BEFORE TESTING: NONE (HEALTHY)
CERTAINTY OF HEART DISEASE BEFORE TESTING: INAPPARENT
MAJOR RECENT THERAPY:  DATE:
    NONE


HEART DIMENSIONS: NORMAL                    HEART VOLUME: N/A


RESTING ECG: NORMAL


THIS EXERCISE TOLERANCE TEST IS AN EXAMPLE OF SHWEX FORMAT

INFORMED CONSENT FOR TESTING AND FOLLOW-UP SIGNED AND WITNESSED: YES

RESTING SBP: 136       RESTING DBP:  76       RESTING HR:  78
MAXIMAL SBP: 154       MAXIMAL DBP:  80       MAXIMAL HR: 162
DELTA SBP:    18       DELTA DBP:     4       DELTA HR:    84
                                               RHYTHM: NSR

*DURATION OF TESTING (FROM START OF STAGE I):  330 SEC.
 SUPPORTED BY HANDRAIL: NO
*ESTIMATED VO2-MAX: 22.4   ML/KG/MIN  (  7  METS)

 CHEST DISCOMFORT: NONE
 MAX SBP * MAX HR/100:  249
 EXERTIONAL HYPOTENSION: NO
*ST DISPLACEMENT: HORIZONTAL OR DOWNSLOPING DEPRESSION
                  PERSISTING >/ 3 MIN
*ARRHYTHMIAS: SINGLE PREMATURE BEAT
 COMPLICATIONS OF TESTING: NONE

 WEIGHTED TALLY OF NORMAL: 5, BORDERLINE: 4, ABNORMAL: 6 ITEMS

 INTERPRETATION OF RESULTS:

 WHERE I=IMPAIRMENT; A=ADAPTATION;
       U=UNDER WEIGHT/AGE; O=OVER WEIGHT/AGE;
       RELATIVE WEIGHT= 100 * IDEAL WEIGHT FOR HEIGHT/ACTUAL WEIGHT;
       RELATIVE AGE= 100 * EQUIVALENT FUNCTIONAL AGE/CHRONOLOGICAL AGE

RELATIVE TO NORM. STD.   60      80      100%    120     140
                         |   |   |   |   |   |   |   |   |
                                          :
REL. WEIGHT:        101%                  O                  WGT:  83 KG
                                          :
REL. AEROBIC CAP.:   60%  IIIIIIIIIIIIIIII                   FAI:   40%
                                          :
REL. LV CAP.:        75%        IIIIIIIIIII                  LVI:   25%
                                          :
REL. HR CAP.:        91%               IIII                  HRI:    9%
                                          :
REL. PERIPH. CAP.:   85%            IIIIIII                  PCI:   15%
                                          :
REL. FUNCT. AGE:    171%                  OOOOOOOOOOOOOOOOO  >50% OF AGE
                                          :


CURRENTLY OBSERVED PRIMARY CHD EVENT RATES FOR HEALTHY MEN
          (PER 100 MEN PER YEAR -- AGES 45-54)

* = PRIMARY EVENTS

            0         5         10        15        20        25
            |         |         |         |         |         |
BY CLINICAL
DIAGNOSIS   *                                                   0.42

BY EXERCISE
PREDICTORS  ********************                               10.42
```

Figure 3.—Computer printout for a 46-year-old-man classified as healthy. However, he has significant risk factors identified and abnormal exercise test responses, with a functional aerobic impairment of 40 percent and significant ST-segment displacement with exercise. On the basis of exercise test responses and the risk factors identified, the probability of subsequent primary events is considerably higher for him than for the average male of his age.

mic ST depression. The important finding of the study was that the presence of these exercise responses was not predictive in the group without conventional risk factors, who had an annual event rate of 0.18 percent. In the small group with one or more conventional risk factors and two or more exercise predictors, the annual event rate was 10.4 percent in men 45 to 54 years old and 13.2 percent in men 55 or older. In those with risk factors, but fewer than two exercise predictors, the annual event rate ranged from 0.24 percent in younger men to 0.67 percent in older men. These results are shown in Table 2 and are illustrated in the computer printout shown in Figure 3.

Primary Coronary Heart Disease Events in Hypertensive Patients Without Heart Disease

In a smaller group of persons with previously diagnosed hypertension, but in whom there was no clinical evidence of heart disease, risk-factor screening and exercise testing were useful in identifying those at high risk of primary coronary heart disease events.[8] The important conventional risk factors were smoking, hypercholesterolemia and a positive family history for myocardial infarction or sudden cardiac death. Three exercise variables were shown to be associated with increased subsequent primary coronary heart disease events. They were chest pain during exercise, failure to attain 80 percent of age-predicted maximal heart rate (HRI greater than 20 percent) and an FAI of greater than 25 percent. These results are shown in Table 3.

The SHW Experience of Sudden Cardiac Death in Persons with Clinical Manifestations of CHD

After nearly three years of follow-up on 1,852 ambulatory men with clinical manifestations of coronary heart disease, it became apparent that the relative risk of sudden cardiac death could be assessed from noninvasive clinical and exercise predictors.[5] The important factors selected by discriminant analysis are shown in Table 4. A multiple logistic function was developed to identify patients with CHD with a two-year survival rate ranging from as high as 98 percent to as low as 54 percent. It is of interest to note that neither chest pain nor ischemic ST depression was a statistically important variable for predicting sudden cardiac death in these patients.

Influence of Aortocoronary Bypass Grafting on Mortality

More recently, the analysis of four years of follow-up of 2,001 men showed that 1,670 had not had coronary operations, while 331 had aortocoronary bypass operations after the initial exercise test.[6] The persons were grouped ac-

TABLE 2.—*Annual Probabilities of Primary CHD Events in Healthy Men**

Age groups (years)	25-44	45-54	≥55
Prior to testing	0.20	0.42	0.92
After risk factor evaluation and exercise testing:			
Risk factors = 0	0.14	0.14	0.58
Risk factors ≥ 1 *and* Exercise predictors < 2	0.24	0.46	0.67
Risk factors ≥ 1 *and* Exercise predictors ≥ 2	..†	10.4	13.2

CHD = coronary heart disease

*Rates/100 men.
†Insufficient numbers to offer a prediction.

TABLE 3.—*Annual Probabilities of Primary CHD Events in Men With Hypertension**

Age group (years)	25-44	45-54	≥55
Prior to testing	1.4	1.6	2.4
After risk factor evaluation and exercise testing:			
With risk factors = 0 *and* Exercise predictors = 0	.7	.8	1.5
Risk factors ≥ 1 *or* Exercise predictors ≥ 1	1.6	1.25	2.5
Risk factors ≥ 1 *and* Exercise predictors ≥ 1	3.7	6.3	4.0

CHD = coronary heart disease

*Rates/100 men.

TABLE 4.—*Variables Selected in Stepwise Discriminant Analysis*

Step		*Multiple* r^2	*F Value*
1	Number of resting ECG abnormalities	0.05	55.2
2	Maximal systolic pressure	0.09	36.3
3	Cardiomegaly	0.11	27.7
4	Duration of exercise	0.12	6.6
5	Height of patient	0.13	6.8
6	Exertional arrhythmia score*	0.13	4.0

ECG = electrocardiographic

*Most severe type present, coded as: 0 if none or only 1; 1 if supraventricular (premature beats, 2 or more not ventricular in origin, or atrial fibrillation); 2 if two or more ventricular premature beats; 3 if multifocal ventricular beat or R on T phenomenon, ventricular in origin; 4 if ventricular tachycardia, and 5 if ventricular fibrillation or cardiac arrest.

cording to the following: (1) presence or absence of myocardial ischemia on exercise testing (angina or ST depression) or (2) left ventricular dysfunction (cardiomegaly; peak systolic blood pressure during exercise less than 130 mm of mercury or duration of exercise of less than three minutes in stage I [which requires expenditure of only four mets of energy]). A significant difference in four-year survival was noted between patients with left ventricular dysfunction who had had operations and those who had not had them (Figure 4). Such a difference was not found in the other groups.

The computer system reports one-year probabilities for secondary coronary heart disease events in men with coronary heart disease based first on age and second on exercise responses (Table 5). Finally an estimate of the possible effect of aortocoronary vein bypass operations on cardiac mortality is given.

Relative risk is of interest, but its more general application is meaningful only when compared with the population subset with the lowest possible risk of future events. The risk should not be related to the average experience of any one population because this reference standard varies substantially with the composition and size of the sample, as well as criteria and duration of follow-up surveillance. Accordingly, the relative risks

TABLE 5.—*Annual Probabilities of Secondary CHD Events in CHD Men**

Age group (years)	25-44	45-54	≥55
Prior to testing	7.4	7.3	7.7
After testing:			
Without exertional myocardial ischemia *or* Left ventricular dysfunction	5.0	5.5	4.9
With exertional myocardial ischemia only	7.6	7.3	7.0
With left ventricular dysfunction only	15.3	13.7	12.7
With exertional myocardial ischemia *and* Left ventricular dysfunction	29.5	15.2	11.9

CHD = coronary heart disease

*Rates/100 men.

TABLE 6.—*Risks of CHD Events Relative to Healthy Men Without Risk Factors*

	Age Group (years)		
	25-44	45-54	≥55
Healthy men			
Risk factors = 0	1	1	1
Risk factors ≥1 *and* Exercise predictors <2	1.7	3.3	1.2
Risk factors ≥1 *and* Exercise predictors ≥2	..	74.4	22.7
Men with hypertension			
Risk factors = 0 *and* Exercise predictors = 0	5.1	5.3	2.6
Risk factors ≥1 *or* Exercise predictors ≥1	11.1	8.9	4.2
Risk factors ≥1 *and* Exercise predictors ≥1	26.1	44.9	6.8
Men with CHD			
Without exertional myocardial ischemia *or* Left ventricular dysfunction	35.9	38.9	8.5
With exertional myocardial ischemia	54.2	51.8	12.2
With left ventricular dysfunction	109.3	97.9	22.3
With exertional myocardial ischemia *and* Left ventricular dysfunction	210.7	108.6	20.9

CHD = coronary heart disease

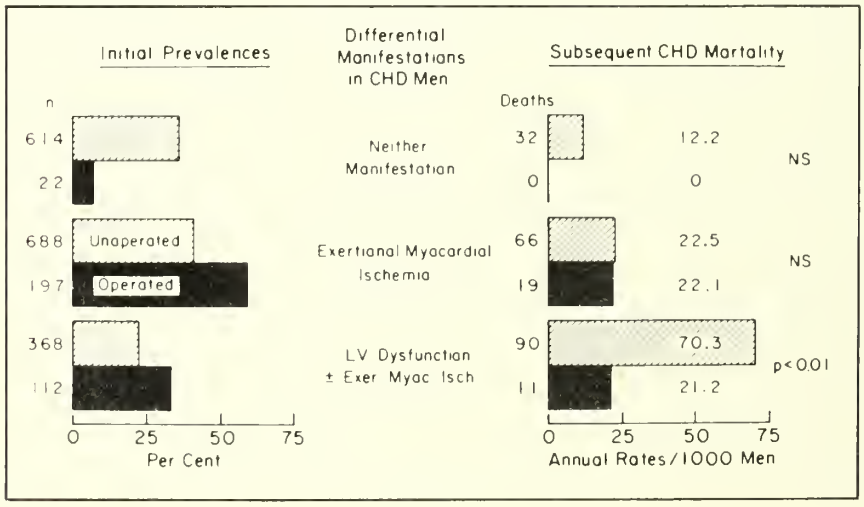

Figure 4.—A comparison of subsequent mortality (expressed as events per 1,000 men at risk) in medically and surgically treated patients. The patients are grouped on the basis of exercise test results (CHD = coronary heart disease). (Reprinted with permission of Circulation and Bruce et al.[6])

for this purpose are related to the age group of healthy men without any of the conventional risk factors. This should facilitate comparison with other population samples similarly defined. The relative risks, defined in this manner, are shown in Table 6. On this basis, the overall risks across all ages for healthy persons, those with hypertension and those with CHD are 2.0, 3.2 and 20.9, respectively. Actually, merely on the basis of clinical classification and age, the relative risk of CHD events is lowest in young healthy men and highest in healthy and in hypertensive men 45 to 54 years old and in men with CHD younger than 55. Using appropriate risk factors and exercise predictors, the relative risk ranges from 1.7 to 74.4 in healthy men, from 13.0 to 108.5 in men with hypertension and from 8.5 to 210.7 in men with CHD. Although the major determinants of CHD risk are age and initial clinical classification of disease, risk factors and exercise responses add substantially to this risk assessment in individual men. This, of course, indicates the additional value of a computer program to evaluate so many variables to provide more precise estimates.

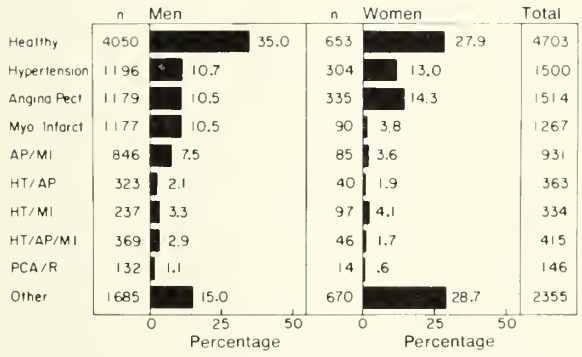

Figure 5.—Clinical classification before exercise testing in 11,194 men and 2,335 women reported to the Terminal Network Registry from March 1975 to July 1978. (AP/MI = angina pectoris and myocardial infarction; HT/AP = hypertension and angina pectoris; HT/MI = hypertension and myocardial infarction; HT/AP/MI = hypertension, angina pectoris and myocardial infarction; PCA/R = prior cardiac arrest with resuscitation; n = numbers.)

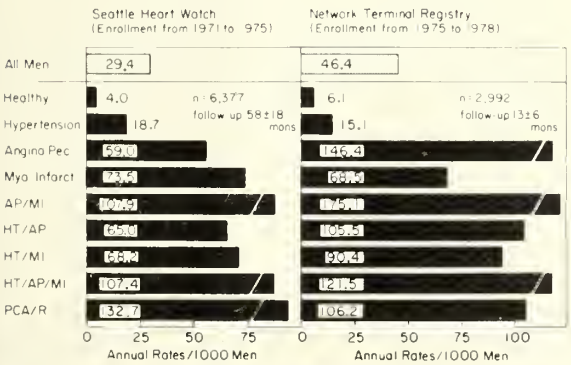

Figure 6.—A comparison of subsequent event rates including cardiac morbidity and mortality in the men enrolled in the Seattle Heart Watch and the Terminal Network Registry. The follow-up in the Terminal Network Registry is considerably shorter than of the Seattle Heart Watch men. (AI/MI = angina pectoris and myocardial infarction; HT/AP = hypertension and angina pectoris; HT/MI = hypertension and myocardial infarction; HT/AP/MI = hypertension, angina pectoris and myocardial infarction; PCA/R = prior cardiac arrest with resuscitation; n = numbers.)

Experience With the Terminal Network Registry

From March 1975 to July 1978, there were 13,529 tests entered in the Terminal Network Registry (Figure 5). There were 11,201 men with a mean age of 49.9 ± 10.6 years and 2,343 women with a mean age of 49.9 ± 12.4. Of these, 38 percent of the men and 30 percent of the women were classified as having coronary heart disease before testing; 35 percent of the men and 28 percent of the women were classified as normal. The remainder had a variety of diagnoses including hypertension, atypical chest pain, valvular heart disease and mitral valve prolapse. Current figures indicate increasing usage of the Terminal Network Registry. In the first six months of 1978, there were 2,936 entries. Figure 1 shows the distribution of cases according to site of testing. The practical clinical value and application of the system to office practice is illustrated by the fact that 40 percent of the cases came from the three private institutions and 25 percent of the cases came from the industrial medical department.

Of the persons enrolled in the Terminal Network Registry, 70 percent represent first entries of symptom-limited exercise data. The remaining entries were follow-up tests and, in the majority of these (16 percent), the clinician felt that there had been no significant change. A smaller percentage (10 percent) of patients had improved, while in the remaining 4 percent, there was deterioration in clinical status as judged by the physician.

In Figure 6 the experience of a follow-up of 2,992 men initially enrolled in the Terminal Network Registry is shown.[12] The results are comparable with those of the early SHW experience in most respects; however, there is a significantly higher rate in persons classified as having angina in the Terminal Network Registry. This may be

due to the much shorter follow-up period. In this follow-up sample, it was possible in the coronary patients to obtain a preliminary evaluation of the multiple logistic function for sudden death.[5] The results were consistent with previous experience, the initial trends being similar.

Conclusion

This study has shown that it is feasible to use computer reporting and interpretation of symptom-limited exercise testing data to present measurements of cardiovascular impairment and to give estimates of probabilities of subsequent primary and secondary coronary heart disease events based on prior SHW experience. It was reported in a previous study that as a result of exercise testing, persons were motivated to modify adverse health habits, and the number of persons reporting change was greater among those who were more functionally impaired.[12] The graphic display of the functional impairment provided by the computer printout may enhance the motivating value of exercise testing, and it is hoped that the presentation of probabilities may assist physicians in their decisions regarding patient management.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MARRIED TO MEDICINE: An Intimate Portrait of Doctors' Wives —Carla Fine. Atheneum Publishers, 597 Fifth Ave., New York, NY (10017), 1981. $12.95.

Certain cultural experiences appeal to the voyeuristic tendencies in all of us. We are captivated by events or people we may not have had experience with except in film, theater, dance and literature. Reading *Married to Medicine* was a little bit like that for me. It dealt with a world that I knew existed yet had had minimal contact with: the life of the typical physician's wife. Carla Fine's documentation of 100 interviews with wives of physicians was appalling on some levels, tragic on others and basically spellbinding reading.

The book reads easily as it draws amply from verbatim quotes from the author's interviews. Rather than attempting to paraphrase selected comments, this approach personalizes the material and adds an element of credibility to the subject matter. After an introductory chapter the book follows the physician through medical school, residency training and finally into practice. The bulk of the work centers on specific topic areas (for example, "The Public Image of Privilege," "The Sanctity of Medicine," "Sex," "Family Life," "The Stresses of Medicine," "Divorce" and "Career Options").

In nearly every chapter the themes and messages are the same. The "husband considers himself a physician above all else." The wife feels somewhat isolated from her husband's world and develops a publicly self-effacing attitude as a result:

> I'm always conscious that if I criticize my husband's compulsive dedication to his work, I will be regarded as a spoiled princess . . . When I have to attend a family gathering or a friend's cocktail party by myself —which is quite often—people will just ooh and aah after they learn my husband's absence is due to the fact that he had to deliver a baby. "How terrific," they'll say. "You must be so proud." Yet if I were married to a lawyer who had stayed home to finish some briefs, their reaction would probably be: "Your husband is really a workaholic. You should get him to relax." I'm in the position of having to smile appreciatively about his accomplishments when deep down I'm really resenting the closeness between my husband and that other woman giving birth. They are sharing a wonderful, glorious experience while I am left alone. If I told other people—except perhaps other doctors' wives—my true feelings, they would be shocked and disgusted.

Fine points out in the chapter entitled "Divorce" that the depth of these feelings is not often discussed between husband and spouse, thus leading to further marital discomfort and occasionally divorce.

Another problematic dynamic is that of the spillover of behavior in various professional settings into family life. Professional deference (rampant for better or worse in most medical environments) becomes an expectation at home for many physicians. They do not see themselves governed by the same rules of conduct as other family members. They expect to be relieved of normal familial responsibilities because they are "too tired" or "work so hard during the day" that they have "little time" to be a nonprofessional even at home.

The portrait of the average American medical family painted in *Married to Medicine* is profoundly disquieting, shades of "The Stepford Wives." The sentiments echoed throughout the book seem not so much repetitive as hauntingly reminiscent of one another. Few cases are mentioned which stray from the traditional model of a modern medical marriage. This oversight is unfortunate since a number of younger physicians who have sought more balanced life-styles currently exist in most medical communities. Nevertheless Fine's effort is an important contribution to the literature on contemporary American medicine. She proves that we can gain understanding of the physician through the words of those closest to him or her (since she writes of female physicians in Chapter 13). Undoubtedly her interviewees felt little constraint in speaking with her so frankly. It is a tragedy that many of their spouses never seek the same depth of understanding that Fine does. They may need to read the book to find it.

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* * *

CURRENT SURGICAL MANAGEMENT OF NEUROLOGIC DISEASE —Edited by Charles B. Wilson, MD, Professor and Chairman, Department of Neurological Surgery, University of California, San Francisco; and Julian T. Hoff, MD, Professor and Vice Chairman, Department of Neurological Surgery, University of California, San Francisco. Longman Inc., 19 West 44th Street, New York City (10036), 1980. 356 pages, $39.50.

This book is somewhat unusual in that it is written on the neurosurgical management of neurologic disease but written for physicians who are not neurosurgeons. As a result, the individual sections are somewhat brief and would be too superficial for practicing neurologists or neurosurgeons or house officers. However, it would be an excellent introduction to neurosurgery for medical students and would also be a valuable means of continuing medical education for physicians who deal with some facets of neurologic disease in their practice.

The general topics covered are congenital disorders, neoplastic disease, vascular disorders, trauma, infection of the central nervous system and acquired disorders such as trigeminal neuralgia. In this regard the book is extremely timely and includes a specific chapter on augmentation of collateral cerebral blood flow, an operation which is being increasingly recognized as a treatment for certain types of intracranial vascular disease.

In general, the chapters are well written and clear, and do not abound with esoteric lingo. The book is well edited and the references are, in the most part, timely and relevant. The editors have done an excellent job in recruiting experts to represent each individual topic covered.

Drs. Wilson and Hoff have provided an up-to-date review of current surgical management of neurologic disease, written in such a way that it should be easily understandable to most physicians. It will be interesting to see how the book is accepted by the audience it has been targeted for.

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Seattle

in memoriam

California Medical Association

ADAMS, WALTER C., JR., Merced. Died June 28, 1981, in Oakland, aged 61. Graduate of Washington University School of Medicine, St. Louis, 1950. Licensed in California in 1951. Dr. Adams was a member of the Merced-Mariposa Medical Society.

FAHEY, JOHN F., Camarillo. Died April 4, 1981, aged 86. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1925. Licensed in California in 1925. MD degree from California College of Medicine, 1962. Dr. Fahey was a retired member of the Los Angeles County Medical Association.

FOLKER, CHARLES W., Santa Barbara. Died in June 1981 in Santa Barbara, aged 53. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1953. Licensed in California in 1954. Dr. Folker was a retired member of the Santa Barbara County Medical Society.

GINSBURG, HYMAN MILTON, Fresno. Died May 24, 1981, aged 75. Graduate of the University of Colorado School of Medicine, Denver, 1928. Licensed in California in 1930. Dr. Ginsburg was a member of the Fresno-Madera Medical Society.

GOETSCH, MARGARET, Glendale. Died May 20, 1981, aged 67. Graduate of the Johns Hopkins University School of Medicine, Baltimore, 1940. Licensed in California in 1940. Dr. Goetsch was a retired member of the Los Angeles County Medical Association.

GOLDSTEIN, LOUIS B., San Francisco. Died June 7, 1981, in San Francisco, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1939. Dr. Goldstein was a retired member of the San Francisco Medical Society.

GRAVES, WILLIAM F., South Pasadena. Died May 25, 1981, in the Angeles National Forest, aged 58. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1952. Licensed in California in 1952. Dr. Graves was a member of the Los Angeles County Medical Association.

LAHRSON, GLENNARD E., Oakland. Died June 24, 1981, in Oakland of heart disease, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. MD degree from California College of Medicine, 1962. Dr. Lahrson was a member of the Alameda-Contra Costa Medical Association.

MAETH, DAVID, Santa Cruz. Died June 13, 1981, in Santa Cruz, aged 84. Graduate of New York Medical College, New York, 1920. Licensed in California in 1923. Dr. Maeth was a member of the Santa Cruz County Medical Society.

MARQUIS, HAROLD H., San Francisco. Died July 13, 1981, in Los Gatos of myocardial infarct, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Dr. Marquis was a retired member of the San Francisco Medical Society.

MARTIN, JAMES RAYMOND, Pasadena. Died June 11, 1981, aged 90. Graduate of the State University of Iowa College of Medicine, Iowa City, 1918. Licensed in California in 1923. Dr. Martin was a retired member of the Los Angeles County Medical Association.

ROSS, DONALD E., Los Angeles. Died June 15, 1981, in Pasadena, aged 88. Graduate of the University of Toronto Faculty of Medicine, 1914. Licensed in California in 1925. Dr. Ross was a member of the Los Angeles County Medical Association.

SHIPMAN, SIDNEY J., San Francisco. Died July 4, 1981, in San Francisco, aged 85. Graduate of the University of Michigan Medical School, Ann Arbor, 1919. Licensed in California in 1921. Dr. Shipman was a retired member and past president of the California Medical Association and the San Francisco Medical Society.

UNDERWOOD, CECIL D., Northridge. Died June 17, 1981, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1928. Licensed in California in 1928. MD degree from California College of Medicine, 1962. Dr. Underwood was a retired member of the Los Angeles County Medical Association.

New Mexico Medical Society

ANGLE, RICHARD M., Santa Fe. Died June 22, 1981, in Santa Fe, aged 63. Graduate of Northwestern University Medical School, Chicago, 1944. Licensed in New Mexico in 1949. Dr. Angle was a member of the Santa Fe County Medical Society.

Utah State Medical Association

MERRITT, BARD A., Salt Lake City. Died June 21, 1981, in Salt Lake City, aged 48. Graduate of the University of Utah College of Medicine, Salt Lake City, 1966. Licensed in Utah in 1967. Dr. Merritt was a member of the Salt Lake County Medical Society.

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New from Janssen Pharmaceutica: Introducing a promising new approach to coccidioidomycosis therapy

NIZORAL™ TABLETS (ketoconazole)

New:

the first and only orally effective, broad-spectrum antifungal agent.

NIZORAL (ketoconazole) is clinically effective against the major yeast and fungal pathogens. For *C. immitis,* the average MIC is less than 1 μg/ml. Absorption of ketoconazole is rapid; mean peak plasma levels of approximately 3.5 μg/ml are reached within 1-2 hours following a single 200 mg tablet. Development of resistance to NIZORAL has not yet been reported.

Effective:

"...a promising new drug for treatment of coccidioidomycosis."[1]

Clinical studies employing 200 to 400 mg NIZORAL per day have shown a combined response rate* of 35% after 26 (median) weeks of therapy; (at this point, however, 69% of patients were still being treated). Most patients were severe and chronic cases, either failures on or intolerant to amphotericin B.[2] (Recommended minimum treatment is 180 days.)

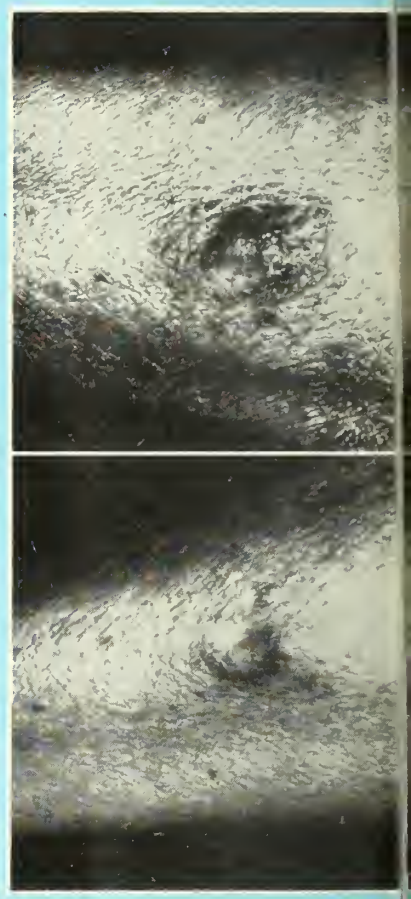
Safe:

"...can be safely administered for prolonged periods..."[3]

Freedom from long-term toxicity permits use of extended therapeutic courses of NIZORAL, when indicated, and provides an extra margin of safety in presumptive antifungal therapy. Long-term administration has revealed no organ toxicity and no consistent changes in important hematological or biochemical values. Infrequent, transient increases in serum liver enzymes have been seen. Adverse reactions were generally minor and only rarely required withdrawal of therapy.

Convenient:

once-a-day oral regimen fosters compliance...facilitates use both in and out of the hospital.



Top: Cutaneous lesion, disseminated coccidioidomycosis, before therapy.

Bottom: Lesion markedly resolved after oral NIZORAL therapy; photographed at 18 month

*Includes cases in remission or markedly improved (no evidence of active disease); both mycological and clinical criteria were considered in measuring overall response.

For further information on NIZORAL write: Professional Services, Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903.

See the facing page for Complete Prescribing Information.

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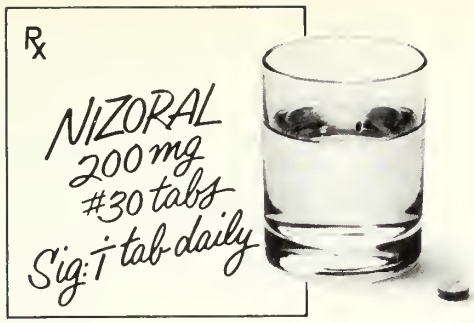
JPI-209

JANSSEN PHARMACEUTICA

NEW orally effective

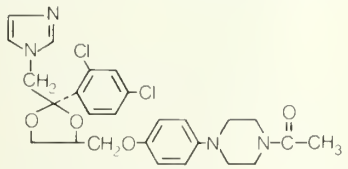
NIZORAL™ TABLETS (ketoconazole)

One tablet a day provides broad-spectrum antimycotic efficacy



DESCRIPTION

NIZORAL™ (ketoconazole) is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole. Ketoconazole is *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:



NIZORAL™ is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44

CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately 3.5 μg/ml are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL™ is converted into several inactive metabolites. The major identified metabolic pathways are: oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99%, mainly to the albumin fraction. Only a negligible proportion of NIZORAL™ reaches the cerebral spinal fluid. NIZORAL™ is a weak dibasic agent and thus requires acidity for dissolution and absorption.

NIZORAL™ is active against clinical infections with *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Phialophora* spp. Development of resistance to NIZORAL™ has not yet been reported.

The following preclinical data are available, however, their clinical significance is unknown. NIZORAL™ is active *in vitro* against dermatophytes, dimorphic fungi, eumycetes, yeasts, actinomycetes, phycomycetes and various other fungi. In animal models, activity has been demonstrated against *Candida* spp., dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Coccidioides immitis*, and *Cryptococcus neoformans*.

Mode of Action: *In vitro* studies suggest that NIZORAL™ impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. Tests in animals suggest this mechanism is not important in mammalian cells.

INDICATIONS AND USAGE

NIZORAL™ is indicated for the treatment of the following fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL™ should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

For the initial diagnosis, the infective organism should be identified, however, therapy may be initiated prior to obtaining laboratory results.

CONTRAINDICATIONS

NIZORAL™ is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

General: In four subjects with drug-induced achlorhydria, a marked reduction in NIZORAL™ absorption was observed. NIZORAL™ requires acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least two hours after NIZORAL™ administration. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a glass or plastic straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Drug Interactions: There is no evidence for clinically significant interaction with oral anticoagulant or oral hypoglycemic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of NIZORAL™ as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames' *Salmonella* microsomal activator assay was also negative.

Pregnancy: Teratogenic effects: *Pregnancy Category C*. NIZORAL™ has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day, (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

Nonteratogenic effects: NIZORAL™ has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered NIZORAL™ during the third trimester of gestation. This occurred when NIZORAL™ was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of NIZORAL™ during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD_{50} of NIZORAL™ given by gavage to the female rat is 166 mg/kg, whereas in the male rat the oral LD_{50} is 287 mg/kg.

Nursing Mothers: Since NIZORAL™ is probably excreted in the milk, mothers who are under NIZORAL™ treatment should not breast-feed the child.

Pediatric Use: Safety in children under two years of age has been documented in a limited number of cases.

ADVERSE REACTIONS

NIZORAL™ is usually well tolerated. Most adverse reactions reported have been mild and transient and have only rarely required withdrawal of therapy.

The most frequent adverse reactions were nausea and/or vomiting, which occurred in approximately 3% of patients. Abdominal pain was reported in approximately 1.2% of patients, pruritus in approximately 1.5% of patients. The following have been reported in less than 1% of patients: headache, dizziness, somnolence, fever and chills, photophobia, and diarrhea. Infrequent, transient increases in serum liver enzymes have been seen.

OVERDOSAGE

In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting dose of NIZORAL™ is a single daily administration of 200 mg (one tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of NIZORAL™ may be increased to 400 mg (two tablets) once daily.

Children:

Children weighing 20 kg or less	50 mg (¼ tablet) once daily
Children weighing 20-40 kg	100 mg (½ tablet) once daily
Children weighing over 40 kg	200 mg (1 tablet) once daily

Generally, treatment should be continued until all clinical and laboratory tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is one or two weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is six months.

HOW SUPPLIED

NIZORAL™ is available as white, scored tablets containing 200 mg of ketoconazole debossed "JANSSEN." They are supplied in bottles of 60 tablets.

U.S. Patent Pending — May 1981

NDC 50458-220-06 (60 tablets)

Manufactured by:
Janssen Pharmaceutica n.v.
B-2340 Beerse, Belgium

For:
Janssen Pharmaceutica Inc.
New Brunswick, New Jersey 08903 USA

References:

1. Brass C, Galgiani JN, Campbell SC, et al: Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. *Reviews of Infectious Diseases* 2 (4): 656-660, 1980. **2.** Data on file, Janssen Pharmaceutica. **3.** Graybill JR, Lundberg D, Donovan W, et al: Treatment of coccidioidomycosis with ketoconazole. Clinical and laboratory studies of 18 patients. *Reviews of Infectious Diseases* 2 (4): 661-673, 1980.

Committed to research...
because so much remains to be done.

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903

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PHYSICIANS WANTED

PULMONARY, ALLERGY, and INFECTIOUS DISEASE subspecialists wanted to join a well-established pulmonary and infectious disease medical group in Northern California. Competitive salary and fringe benefits. Send CV to Box AIM, 6226, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTITIONER to join two-man incorporated active practice in community 6,000, warm climate central Washington State. Need third man, preferably certified Family Practice and interested in OB. Full membership after six months (salary). Paid malpractice, health insurance, vacation time, CME leave, etc. Will help re-locate. No better hunting, fishing, skiing, golfing, boating anywhere. Thirty-bed community hospital; full privileges. Write: Paul G. Kinney, MD, P.O. Box 636 (508 West Division), Ephrata, WA 98823. Phone: Collect (509) 754-3563.

PIERCE COUNTY MEDICAL BUREAU, INC., the Blue Shield Plan in Tacoma, Washington, has an opening for a full-time Assistant Medical Director. Desirable that applicant be under 50 years of age. Retirement plan, life insurance, medical-surgical-hospital-dental plan—all paid by employer. Salary open. Send résumé and salary desired to Laurence J. Evoy, President, Pierce County Medical Bureau, Inc., 1114 Broadway Plaza, Tacoma, WA 98402.

GENERAL SURGEON—Two general surgeons in practice in Idaho are seeking a University trained associate for the practice of General, Peripheral Vascular surgery. Please send curriculum vitae to Box 6219, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

NON-INVASIVE CARDIOLOGIST to join a young cardiologist in a growing consultation practice in Central Valley California. Expertise in non-invasive cardiovascular procedures required. Experience in cardiac rehabilitation desirable. Reply with curriculum vitae to Box 6238, Western Journal of Medicine, 731 Market St., San Francisco 94103.

TEXAS EMERGENCY MEDICINE: Clinical positions available in moderate volume emergency department located in El Paso. Competitive hourly guarantee plus bonus based on productivity. Flexible scheduling; paid professional liability insurance provided. For details, send credentials in confidence to Sue Haberman, 845 East Arapaho, Suite A-1, Richardson, TX 75081; or call collect (214) 669-0606.

ORTHOPEDIST NEEDED. Join established orthopedist full time or as semi-retirement. Compensation negotiable. Desirable area. Contact: Mary Bradshaw, (415) 376-0762.

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INTERNISTS NEEDED both solo and group practices in Kennewick, Washington. Call collect —Raymond Kerr, MD; (509) 582-5137.

INTERNIST and GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guaranteed with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 E. 4th No, Logan, UT 84321.

RENOWNED MULTISPECIALTY GROUP of 28 physicians located in south-central Kansas is seeking board eligible/certified additions for the following specialties: General Internal Medicine, Pulmonary Medicine, Gastroenterology, General Surgery, and Pathology. Rotating call schedule. Guaranteed salary plus incentive plan. Association after 1 year. Reply Box 6228, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CALIFORNIA, SAN JOSE: Primary Care Physician with experience in minor trauma and Peds. wanted to staff ambulatory care clinic at large teaching hospital in San Francisco Bay Area. Flexible hours, independent contractor status with hourly compensation. For further details, please call or write: Eve Campbell, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Tel: (408) 293-8881.

CALIFORNIA, SAN JOSE: Experienced Emergency Physician with Spanish-speaking ability preferable, wanted to join our group practicing in San Jose at a University-affiliated medical center and two community hospitals. Total patient volume of 90,000; fee-for-service compensation. If interested, send CV or contact: James B. Lane, MD, 1541 The Alameda, 2nd floor, San Jose, CA 95126. Phone (408) 293-8881.

HEMATOLOGIST-ONCOLOGIST needed for busy, aggressive practice of same in Northern California community, one and a half hours from San Francisco. Available immediately. Send CV to Box 6222, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTICE-GENERAL PRACTICE—Excellent opportunity for practice in Central Calif. New modern Clinic facilities available late 1981. Salary and office space negotiable. Chowchilla, California is a rural community 40 miles from a metropolitan area, 2 hours from the snow-capped Sierras, 2 hours from San Francisco, and less than 2 hours from California's sunny beaches. For further information write to: Russ McSwain, Administrator, Chowchilla District Memorial Hospital, P.O. Box 1027, Chowchilla, CA 93610.

FAMILY PRACTITIONERS NEEDED to practice with 280-man multispecialty group. Board certified or eligible. Salary negotiable. Excellent fringe benefits. Contact: James O. Farley, MD, Permanente Medical Group, P.O. Box 254999, Sacramento, CA 95825 or call collect (916) 486-5103. An Equal Opportunity Employer.

FAMILY PRACTICE PHYSICIAN. Board-certified, OB-experienced, to establish new practice in medically-underserved area Berry Creek, rural northern Calif. Sierra Nevada foothills. Federally-funded BCHS site provides facility, equipment, support staff, operating costs. With dedication and effort, potential excellent for self-sustained operation within 2-5 years. Starting salary $25,000. Ideal living, good schools, summer and winter recreation. Send Curriculum vitae to: R. W. Kearney, Yuba Feather Rural Health Systems, Box 142, Brownsville, CA 95919, or call (916) 675-2733.

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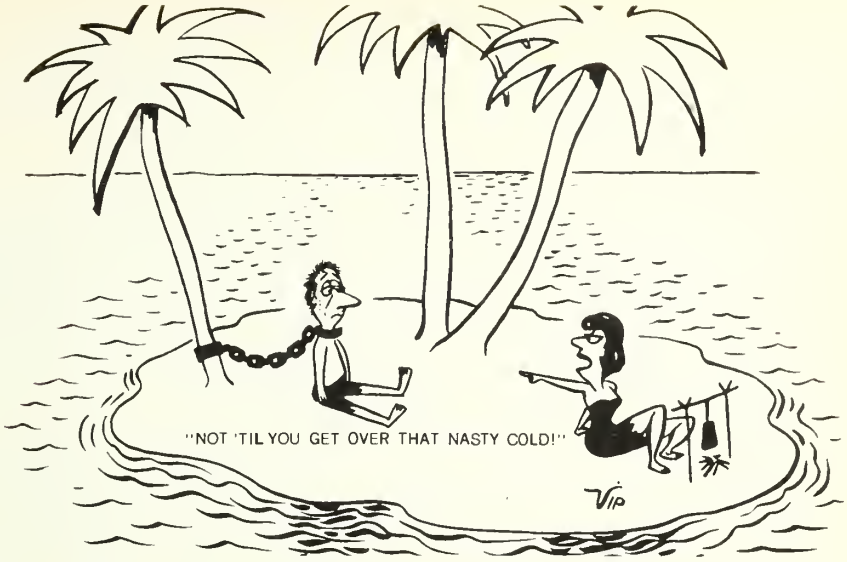
(Continued on Page 43)



Citra® Forte Syrup stops stubborn coughs

...and with an Rx for CITRA® FORTE Capsules you can provide the additional benefits of helping your patients "feel well" for the duration of their colds—free of most cold symptoms.

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- Rx • Triva Jel... Provides continuous action
- Rx • Triva Combination... Jel and Powder kit

CITRA® FORTE SYRUP

Each 5cc contains:

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg
Ascorbic Acid	30 mg
Pheniramine Maleate	2.5 mg
Pyrilamine Maleate	3.33 mg
Potassium Citrate	150 mg

PRECAUTIONS Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.

CITRA® FORTE CAPSULES

Hydrocodone Bitartrate (WARNING: May be habit forming)	5 mg
Ascorbic Acid	50 mg
Pheniramine Maleate	6.25 mg
Pyrilamine Maleate	8.33 mg
Chlorpheniramine Maleate	1 mg
Phenylephrine HCl	10 mg
Salicylamide	227 mg
Caffeine Alkaloid	30 mg
Acetophenetidin	120 mg

PRECAUTIONS Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients. CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.

WARNING This preparation may damage the kidneys when used in large amounts or for a long period of time. Use with caution in greater than recommended dose or regularly for longer than 10 days (Acetophenetidin).

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13260 Moore Street,
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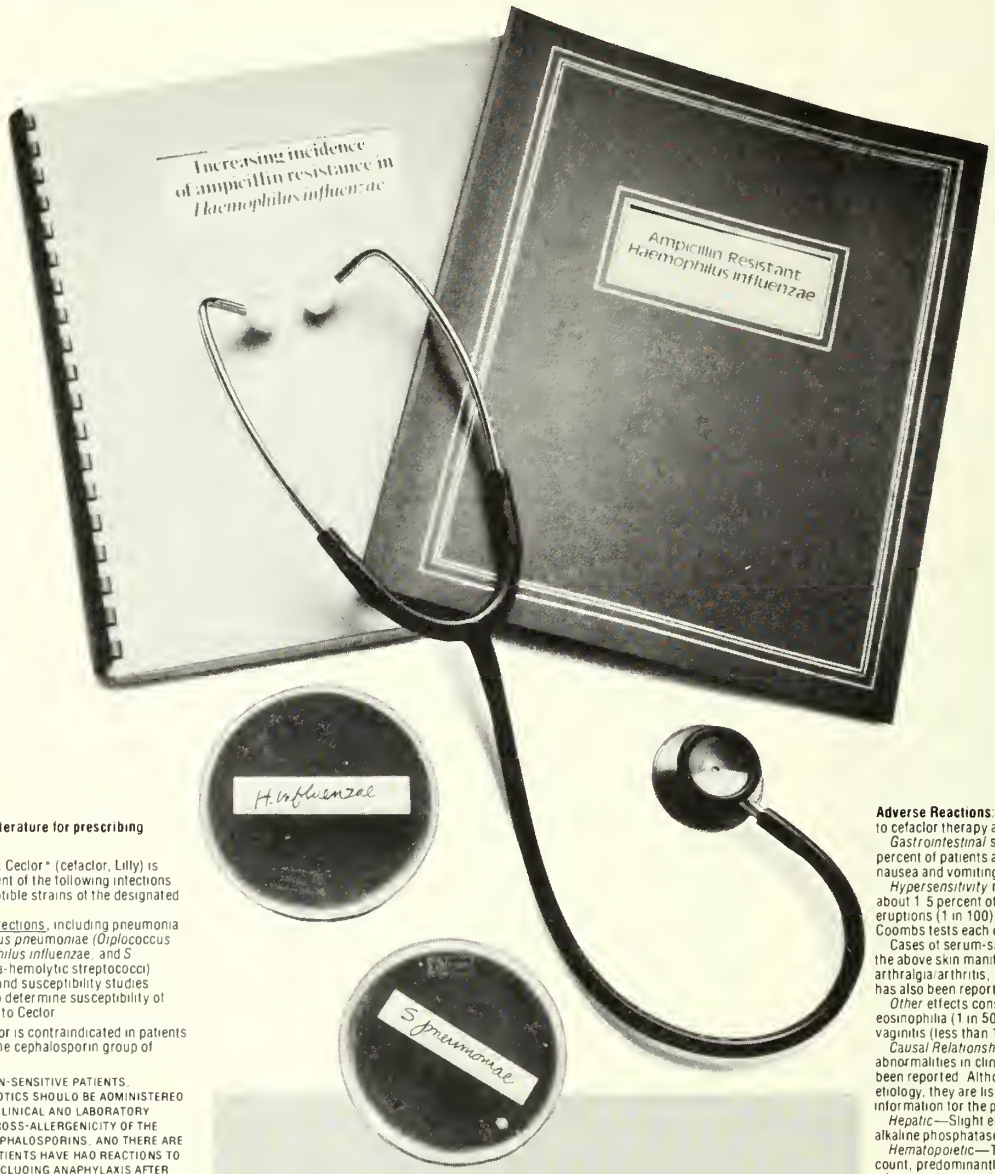
An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER PARENTERAL USE)

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g , pressor amines, antihistamines, or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly)

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90)

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients

Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported Anaphylaxis has also been reported

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200) [103060R]

* Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae* *

Note Ceclor* (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

References

1 Antimicrob Agents Chemother , *8* 91, 1975
2 Antimicrob Agents Chemother , *11* 470, 1977
3 Antimicrob Agents Chemother , *13* 584, 1978
4 Antimicrob Agents Chemother., *12* 490, 1977
5 Current Chemotherapy (edited by W Siegenthaler and R Luthy), II 880 Washington, D.C. American Society for Microbiology, 1978
6 Antimicrob Agents Chemother , *13* 861, 1978
7 Data on file, Eli Lilly and Company
8 Principles and Practice of Infectious Diseases (edited by G L Mandell, R G Douglas, Jr , and J E Bennett), p 487 New York John Wiley & Sons, 1979

Lilly

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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(Continued from Page 37)

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WANTED—Physician to cover Family Medicine-Allergy office part-time during the week & Saturdays. On-going opportunity. Send short résumé to Box 6237, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GP needed in town near Sacramento, Calif. Rapid growth area. New office space available. Call Drs. Klem or Guarcello, (916) 652-0449.

FAMILY PHYSICIAN—Board certified or qualified to join active practice of two family physicians and one nurse practitioner in picturesque, small community, Western Washington State on the waters of Puget Sound surrounded by Olympic mountains, one hour from Seattle. Practice includes obstetrics. Salary competitive, base guaranteed plus productivity. Fringe benefits excellent. Send CV to Almond Clinic, Richard Auerbach, MD, George Kina, MD, P.O. Box 188, Poulsbo, WA 98370.

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(Continued on Page 45)

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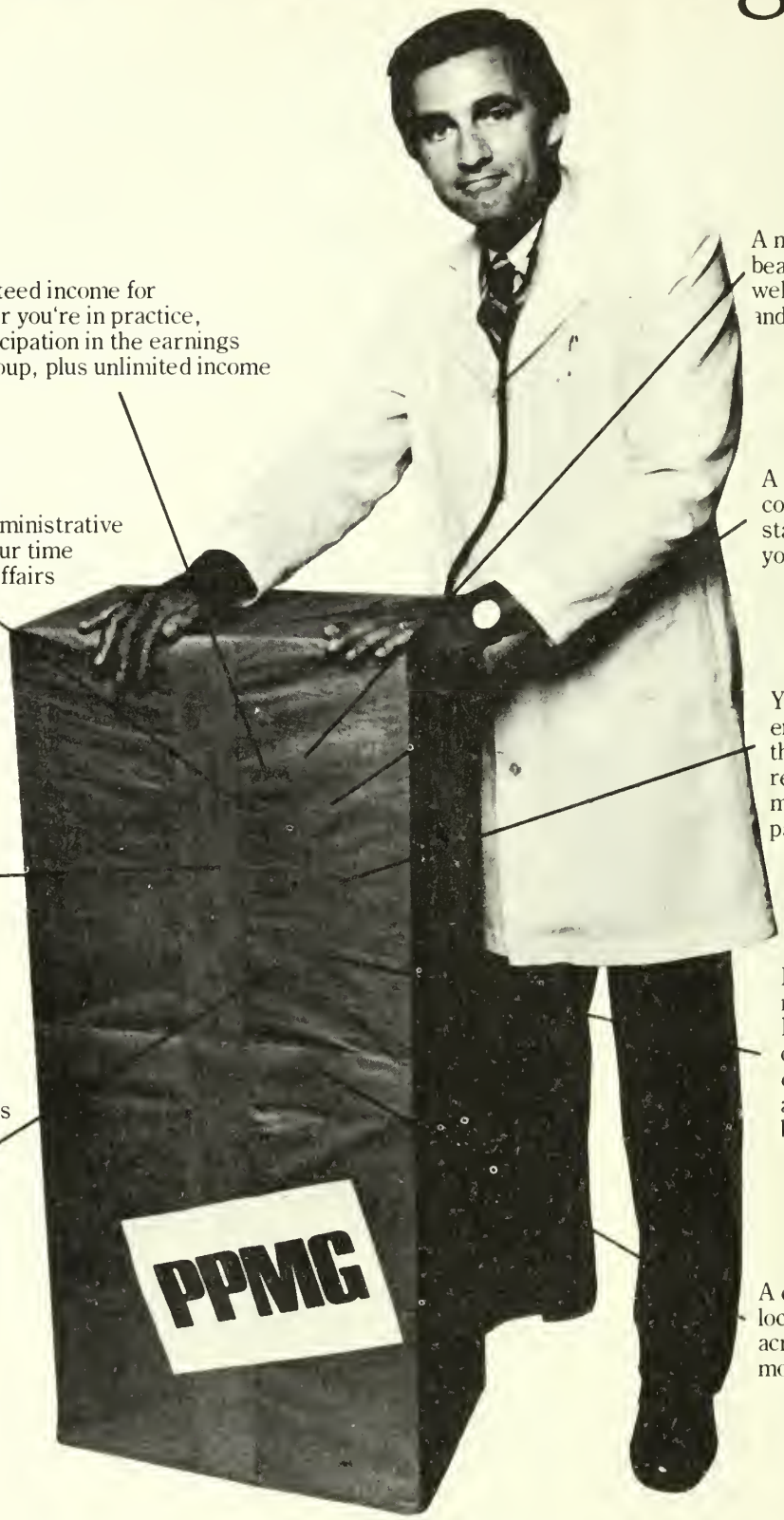

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ANESTHESIOLOGIST, board certified, 15 years experience; desires position on West Coast or Northwest states near water. May be solo, group, or teaching-related. Licensed Oregon and Washington. Box 6234, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GASTROENTEROLOGIST/INTERNIST: 32-year-old ABM certified, GI eligible skilled in all endoscopic procedures with excellent references desires academic-oriented private practice opportunity for July 1982. Box 6239, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN ASSISTANT: 1981 graduate, BA, BS, 10 years of health care experience. California licensed, NCCPA board eligible-October exam. Seeking San Francisco Bay Area position. Reply Box 6243, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

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PREVENTIVE MEDICINE, diplomate, 44, MPH, author, subspecialty TB, substance abuse, some GP, bilingual, seeks part- or full-time clinical and/or admin. post, public or private. Box 1613, Santa Monica, CA 90406.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

TO MAKE THE PATIENT READY FOR ANESTHESIA: MEDICAL CARE OF THE SURGICAL PATIENT—Edited by Leroy D. Vandam, MD, Peter Bent Brigham Hospital and Harvard Medical School, Boston. Addison-Wesley Publishing Company, Inc., Health Sciences Div., 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 245 pages, $24.95.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY—CLINICS IN DIAGNOSTIC ULTRASOUND: Volume 4—Edited by Joseph A. Kisslo, MD, Associate Professor of Medicine, Assistant Professor of Radiology; Director, Clinical Cardiology Laboratory, Duke University Medical Center, Durham, North Carolina. Longman Inc., 19 West 44th Street, New York (10036), 1980. 204 pages, $20.50.

QUALITY AND ACCOUNTABILITY—A New Era in American Hospitals—Stanley A. Skillicorn, MD, Director of Medical Education, San Jose, California. Editorial Consultants, Inc., 655 Sutter Street, San Francisco (94102), 1980. 144 pages, $14.00.

WILLIS'S OXFORD LECTURES—Edited and introduced by Kenneth Dewhurst, TD, DPhil, FRCPsych. Standford Publications, Manor House, Sandford-on-Thames, Oxford OX4 4YN, England. 181 pages, Price: 9 English Pounds, limited to 750 copies.

SEXUAL REHABILITATION OF THE UROLOGIC CANCER PATIENTS—Edited by Andrew C. von Eschenbach, MD, Department of Urology, and Dorothy B. Rodriguez, RN, MS, Department of Nursing, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 322 pages, $39.95.

SODIUM IN MEDICINE AND HEALTH—Campbell Moses, MD, Salt Institute, 206 North Washington Street, Alexandria, Virginia (22314), 1980. 126 pages, $3.95.

WHAT TO DO WHEN YOU THINK YOU CAN'T HAVE A BABY—Karol White. Doubleday & Co., 245 Park Ave., New York City (10017), 1981. 215 pages, $11.95.

SURVEY OF FUNCTIONAL NEUROANATOMY—Bill Garoutte, PhD, MD, Professor of Anatomy and Neurology, University of California, San Francisco. Jones Medical Publications, 355 Los Cerros Drive, Greenbrae, CA (94904), 1981. 217 pages, $9.95 (paperback).

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December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

December 11-13—**Cardiology for the Primary Care Physician.** UCD. Friday-Sunday.

December 12—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

January-March—**Endocrinology for the Practicing Internist.** UCLA. Wednesday evenings.

January 8-15—**6th Annual Echocardiography Conference.** Honolulu Medical Group Research and Education Fndn. at Kauai Surf Resort, Kauai. One week. 32 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

January 9-15—**Gastrointestinal and Hepatic Diseases.** Honolulu Medical Group Research and Education Fndn. at Hyatt Regency, Maui. Saturday-Friday. 21 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9-16—**Endocrinology and Metabolism.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 16-23—**Nephrology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $425.

January 20-22—**Conference on Nephrology.** UCSD at Hilton, San Diego. Wednesday-Friday.

January 27-29—**Echocardiography: An Introductory Course for the Practicing Physician.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2-6—**What Is Ahead in Lung Diseases for the 80's.** USC at Death Valley. Tuesday-Saturday.

February 3-5—**Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 6—**Clinics in Medicine—Rheumatology.** PMC. Saturday. 3 hrs. $40.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 18-20—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 18-20—**Controversies and Problem Solving With Endoscopy—An Update.** So. Calif. Society for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 18 hrs. Contact: Dr. Albert Dreskin, 13652 Cantara St., Panorama City 91402.

February 20-27—**Cardiology.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Sunday-Tuesday.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

March 3-6—**Immunology and the Clinical Practice of Allergy—6th Annual Course.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs.

March 5—**Diabetes.** UCD at Red Lion Inn, Sacramento. Friday.

March 7-10—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday.

March 10—**Hypothyroidism—Unmasked.** LLU. Wednesday. 4 hrs. $30.

March 11-13—**Therapeutic and Diagnostic Uses of the Cardiac Catheter.** Am. College of Cardiology at Bonaventure Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 12-13—**Stress Testing Today and Tomorrow.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

March 19-20—**Non-Invasive Cardiology Conference.** Clairemont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 22-April 2—**30th Annual Review of Internal Medicine.** USC. 12 days.

Kennamer Fellows Program in Internal Medicine. UCLA. One and two-year fellowships available, beginning July 1, 1982. Applications due by November 1, 1981. Contact: David H. Solomon, MD, Dept. of Medicine, UCLA Center for the Health Sciences, Los Angeles 90024.

OBSTETRICS AND GYNECOLOGY

October 14-18—**Pacific Coast Fertility Society—29th Annual Scientific Meeting and Postgraduate Courses.** Marriott's Rancho Las Palmas Resort, Rancho Mirage. Wednesday-Sunday. 21 hrs. Contact: Dir. of Med. Ed., PCFS, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

October 17—**Preventing Birth Defects.** UCD and March of Dimes at Sierra Inn, Sacramento. Contact: UCD.

October 26-30—**11th Annual Review Course in Obstetrics and Gynecology.** USC at Hilton, Pasadena. Monday-Friday.

October 26-31—**Review Course in Clinical Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center-UCI Center for Health Education

at Sheraton, Newport Beach. Monday-Saturday. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 7-9—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 14-16—**Perinatology.** UCSD at Holiday Inn at Embarcadero, San Diego. Monday-Wednesday.

January 9-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $395.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

February 6-7—**Los Angeles OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 8-12—**37th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 14-17—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

PEDIATRICS

October 18—**The Hearing Impaired: Identification, Counseling and Rehabilitation.** Peninsula Hospital and San Mateo Co. Office of Education at Peninsula Hospital, Burlingame. Sunday. Contact: Les Demme, Peninsula Hosp. and Med. Ctr., 1783 El Camino Real, Burlingame 94040. (415) 697-4061.

October 23-24—**New Directions in Care for the Handicapped Child.** State Dept. of Special Education and Northern Calif. Chap., Am. Academy of Pediatrics, at Fresno Community Hospital, Fresno. Friday-Saturday. $75. Contact: Peter Miller, MD, Marin Civic Ctr., Rm. 280, San Rafael 94903. (415) 499-6877.

October 23-24—**The Pediatrician's Role in the Management of Neurological and Neurosurgical Problems.** Children's Hospital Medical Center of Northern Calif. at Doubletree Inn, Monterey. Friday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

October 24—**Pediatric Seminar, Asthma: Principles and Management.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 453-8696 or (916) 486-2690.

December 4-6—**Kids Have Bones, Too.** UCD at Del Monte Hyatt, Monterey. Friday-Sunday.

December 12—**Managing Pediatric Emergencies.** No. Calif. Chapter, Am. Academy of Pediatrics, at Union Square Holiday Inn, San Francisco. Saturday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

PSYCHIATRY

October 22-23—**Mental Health Issues of the Individual with a Developmental Disability—An Intensive Seminar on Treatment Techniques and Strategies.** Hope Rehabilitation Services and San Jose State Univ. at Rickey's Hyatt House, Palo Alto. Thursday-Friday. Contact: Bonnie Bernell or Fay Sells, HRS, 1539 Parkmoor Plaza, San Jose 95128. (408) 998-4673.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** UCD at Red Lion Inn, Sacramento. Saturday. 7¼ hrs. $75.

December 12-19—**Psychiatry and the Marathon.** Univ. of Washington School of Medicine at Honolulu. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 21-26—**Psychiatric Symposium.** Continuing Medical Education, Inc., and Western Medical Center at Maui Surf Resort, Maui. Thursday-Tuesday. 24 hrs. Contact: CME, Inc., 2030 E. 4th St., #113, Santa Ana 92705. (714) 547-5186.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

January 31-February 4—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 19-20—**Heinz Von Foerster on Cybernetics, Language and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

RADIOLOGY AND PATHOLOGY

October 29-30—**Laboratory Diagnosis in Clinical Practice.** UCSF. Thursday-Friday.

October 31—**GYN Pathology.** USC. Saturday. 6 hrs. $60.

November 24—**Use of Antimicrobial Agents Old and New.** UCD at Red Lion Inn, Sacramento. Tuesday.

February 3-5—**New Directions in Clinical Laboratory Assays: 4th Immunology Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 18 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 10—**Pulmonary Function Tests and Blood Gas Interpretation.** LLU. Wednesday. 4 hrs. $30.

March 3-5—**Sierra Radiology Conference—3rd Annual.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at North Lake Tahoe. Wednesday-Friday. 18 hrs. $265. Contact: Michael H. Reid, PhD, MD, Sac. Rad. Research and Ed. Fndn., P.O. Box 161112, Sacramento 95816.

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section. UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

October 15-17—**New Horizons in Knee and Hip Surgery.** UCLA. Thursday-Saturday.

October 16-17—**Fracture Bracing Workshops.** USC at University Hilton, Los Angeles. Friday-Saturday. 17 hrs. $375.

November 7-8—**Clinical Application of Evoked Potentials.** UCSF. Saturday-Sunday.

November 11-15—**Pediatric Surgery of the Head and Neck: A Frontier Symposium.** Institute for Medical Education and Research at Silverado County Club, Napa. Wednesday-Sunday. 20 hrs. Contact: Inst. for Med. Ed. and Research, 135 Dickinson St., San Diego 92103. (714) 272-3126.

November 11-15—**The Spine.** USC at Canyon Hotel, Palm Springs. Wednesday-Sunday. $400.

November 12-14—**Techniques in Urinary Tract Surgery.** American Urological Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Office of Education, AUA, P.O. Box 1129, Aspen, CO 81611.

November 17-20—**U.S. Section of International College of Surgeons.** Hotel del Coronado, Coronado. Tuesday-Friday. Contact: George Evashwick, MD, 204 Roswell Ave, Long Beach 90803.

November 19-20—**Critical Decisions in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Friday. 12 hrs. $200. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., Rm. 2049, P.O. Box 38750, Los Angeles 90048. (213) 855-5547.

December 2-4—**Invasion of the Cornea and Lens.** UCSF. Wednesday-Friday.

December 2-5—**Society for Office Based Surgery—3rd Annual Meeting.** Jointly sponsored by Sharp Memorial Hospital at Vacation Village Hotel, San Diego. Wednesday-Saturday. $75, members; $125, nonmembers. Contact: Purvis L. Martin, MD, Soc. of Office Based Surgery, P.O. Box 9494, San Diego 92109.

December 3-6—**Bone Grafting: Biology and Application.** Plastic Surgery Research Foundation at Hyatt Islandia, San Diego. Thursday-Sunday. 17 hrs. $275. Contact: Jack C. Fisher, MD, P.O. Box 33387, San Diego 92103.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

January 15-16—**Vitrectomy Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Stereotactic Vitreous Microsurgery.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

January 30-February 6—**Office Urology for Urologists.** Univ. of Washington School of Medicine at Hyatt Regency, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 10-12—**Traumatic and Congenital Hand Surgery.** UCLA. Wednesday-Friday.

February 13-20—**Plastic Surgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 28-March 3—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Wednesday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

March 1-5—**Surgical Forum.** Society of Graduate Surgeons at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 4-5—**13th Annual Lecture and Postgraduate Seminar—Pediatric Ophthalmology and Strabismus Update.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

March 28-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Sunday-Wednesday.

OF INTEREST TO ALL PHYSICIANS

October 16—**2nd Annual Neuroscieuces Symposium: Current Concepts for Non-Neurologists.** Sutter Community Hospitals at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

October 17-18—**The Healing Brain: Who Stays Healthy.** UCSF Cont. Ed. in Health Sciences at Sheraton-Palace, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 18-23—**Recognition and Management of Diving Casualties.** UCSD at Travelodge, Harbor Island, San Diego. Sunday-Friday.

October 19-22—**British Medical Association Congress.** Town and Country Hotel, San Diego. Monday-Thursday. 10 hrs. through UCSD. Contact: Mr. G. Denney, Assoc. Exec. Dir., San Diego Co. Med. Soc., 3702 Ruffin Rd., San Diego 92123. (714) 565-8888.

October 22-24—**West Coast Counties Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 23—**Love Is Ageless: A Seminar on Sexuality and Aging.** UCLA. Friday. 13 hrs. $75.

October 24—**Bio-Ethical Issues and the Terminally Ill.** Cypress Foundation, Hospice of the Monterey Peninsula, Central Coast Cancer Council and Monterey Co. Medical Society at Doubletree Inn, Monterey. Saturday. 5 hrs. $65. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1835.

October 24—**Brief Course in Psychotherapy for Practicing Physicians: Office Management of Sadness and Its Variations.** See Psychiatry, October 24.

October 24-25—**5th Annual Symposium on Aging.** UCSF Cont. Ed. in Health Sciences at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. $125. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

October 25-28—**California Academy of Family Physicians—Annual Meeting.** Masonic Auditorium, San Francisco. Sunday-Wednesday. Contact: William Rogers, CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

October 28-30—**Workshops in Clinical Hypnosis.** USCD at Village Inn, La Jolla. Wednesday-Friday.

October 31—**The Medical Consequences of Nuclear Weapons and Nuclear War.** UCLA at Bonaventure Hotel, Los Angeles. Saturday. 6 hrs. $45.

October 31—**Introduction to Traditional Chinese Medicine.** PMC. Saturday. 7 hrs. $125.

November 1-5—**American Public Health Association—109th Annual Meeting.** Bonaventure Hotel, Los Angeles. Sunday-Thursday. Contact: APHA, 1015 15th St., NW, Washington DC 20005.

November 1-6—**American Congress of Rehabilitation Medicine and American Academy of Physical Medicine and Rehabilitation.** Town and Country, San Diego. Sunday-Friday. Contact: Creston C. Herold, Exec. Dir., 30 N. Michigan Ave., Suite 922, Chicago 60602. (312) 236-9512.

November 2-6—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $325.

November 10-February 9—**Foundations of Traditional Chinese Medicine.** PMC. Tuesday evenings.

November 14-15—**In Pursuit of Wellness.** UCSF Cont. Ed. in Health Sciences at UCLA. Saturday-Sunday. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

November 15—**Dilemmas With Drugs in Clinical Practice.** Granada Hills Community Hospital and UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 16-20—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

December 4—**Nutritional Support: The Challenge for the Seriously Ill Patient.** Daniel Freeman Memorial Hospital and Marina Mercy Hospital at Daniel Freeman Mem. Hosp., Inglewood. Friday. 7 hrs. $60. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Mem. Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 3427.

December 4-6—**Sports Medicine Conference—Athletes and Health.** UCSF at El Rancho Racquet Resort, Sacramento. Friday-Sunday. 17 hrs. $125.

December 4-11—**Behavioral Medicine and Primary Care in the 80's.** Professional Institutes and Univ. of So. Carolina School of Medicine at Ilikai Hotel, Honolulu. One week. 16 hrs. $300. Contact: Jeri McClain, USC School of Medicine, Office for Academic Affairs, Columbia, SC 29208. (803) 777-7470.

December 9-12—**Symposium on Endurance Physiology.** Honolulu Medical Group Research and Education Foundation at Moana and Surfrider Hotels, Honolulu. Wednesday-Saturday. 16 hrs. Contact: Honolulu Med. Grp. Research and Ed. Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 16—**Herpes Simplex: Clinical Practice and Research.** UCSF Cont. Ed. in Health Sciences at Fort Mason Conference Center, San Francisco. Saturday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 3-5—**Neurology for Non-Neurologists.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 6-7—**Immunology for the Family Physician.** UCLA. Saturday-Sunday.

February 7-12—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Friday.

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for

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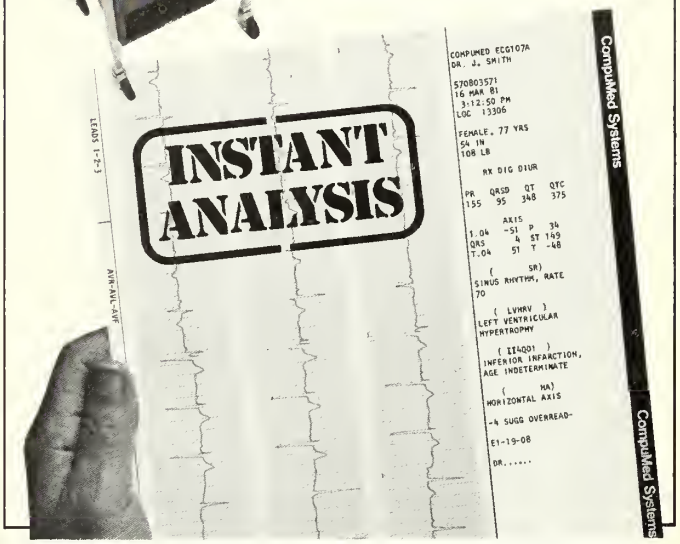

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970; Section 3685, Title 39, United States Code, for THE WESTERN JOURNAL OF MEDICINE, published monthly at San Francisco, California, for September, 1981.

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3. Publisher: California Medical Association, 731 Market Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 731 Market Street, San Francisco; Managing Editor, David Greer, 731 Market Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 731 Market Street, San Francisco, California (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total, 44,474; paid circulation by mail subscription, 43,154; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 454; total distribution, 43,608; office use, leftover, unaccounted, spoiled after printing, 866; total net press run, 44,474. Single issue nearest to filing date, September, 1981: Total 44,660; paid circulation by mail subscription, 43,523; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 313, total distribution, 43,836; office use, leftover, unaccounted, spoiled after printing, 824; total net press run, 44,660. David Greer, Managing Editor.

Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

March 1-2—**Treatment Issues in Geriatrics.** Western Gerontological Society and Washington State Psychiatric Assn. at Town and Country Hotel, San Diego. Monday-Tuesday. Contact: Barbara Freda, WGS, 785 Market St., Suite 1114, San Francisco 94103. (415) 543-2617.

March 10-13—**Optimal Health: A Guide for Practicing Physicians.** Scripps Clinic and Research Fndn. at La Costa Resort Hotel, Carlsbad. Wednesday-Saturday. 22 hrs. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

March 12-17—**California Medical Association—111th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

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Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

See Washington Listings, October 16-18, 1981.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category 1 credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

April 15-17—See Washington Listings.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 8-10—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. UNM Medical School Auditorium. 4 credit hours, also AAFP Prescribed. Contact: Jonathan Abrams, MD, Division of Cardiology, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-4253.

October 9-10—**Southwest Regional Diabetes Symposium.** Albuquerque. Friday-Saturday. Albuquerque Hilton Inn. 8 credit hours. Contact: David Feirer, New Mexico Affiliate Inc., American Diabetes Association, 525 San Pedro Drive, NE, Suite 100, Albuquerque, NM 87108. (505) 266-5716.

October 22-24—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: Barry W. Ramo, MD, 201 Cedar SE, Albuquerque, NM 87106. (505) 242-2796.

October 30—**Infections Disease Update 1981.** Albuquerque. Wednesday. 4 credit hours, also AAFP Prescribed. Contact: Martha McPherson, Pfizer Laboratories Division, Pfizer Inc., 235 East 32nd Street, New York, NY 10017, (212) 573-7285; Or New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 6—**Los Alamos Council for Cancer Annual Symposium for Colon Cancer.** Los Alamos. Friday. 16 credit hours. Contact: Philip H. Newman, MD, FACS, Los Alamos Surgical Associates Ltd., Los Alamos, NM 87544. (505) 662-3383.

November 13-14—**Interim Meeting, New Mexico Medical Society.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Scientific Program: **Oncology for the Eighties.** 7 credit hours, also AAFP Prescribed. Contact: New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 17-21—**The Grand Canyon Conference on the Treatment of Addictive Behaviors.** South Rim of Grand Canyon. Tuesday-Saturday. Grand Canyon National Park Lodges. Hour-for-hour credit. Contact: T. P. Bouble, Conference Coordinator, Division of Continuing Education & Commity Services, University of New Mexico, Albuquerque, NM 87131. (505) 277-2931.

December 11-12—**Annual Meeting New Mexico Chapter American College of Physicians and New Mexico Chapter American Society of Internal Medicine.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. Program and credit hours to be announced. Contact: Robert J. Weiler, MD, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7178.

February 22-26—**Taos Medical Symposium—Sports Medicine.** Taos. Monday-Friday. Kachina Lodge. 20 credit hours, also AAFP Prescribed. Contact: Dale A. Gray, MD, Taos Medical Symposium, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

February 26-28—**10th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 13 credit hours, also AAFP Prescribed. Contact: American Lung Association of New Mexico, 216 Truman NE, Albuquerque, NM 87108. (505) 265-0732.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 20 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 8-12—**Thirteenth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

SURGERY

November 20—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

October 29-30—**Sommer Lecture Series.** Portland. Thursday-Friday. Red Lion Motor Inn-Portland Center. For additional information please contact: Sondra Gleason, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201 (503) 226-1555.

November 12-13—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion at Jantzen Beach. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

December 4-5—**Urology for the Non-Urologist.** Portland. Friday-Saturday. Red Lion-Downtown. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

October/November—**Medical Effects of a Nuclear War** (Sponsor: University of Utah). Salt Lake City. Date: To be announced. University of Utah campus. Credit, Fee: To be announced. Contact: Chase N. Peterson, MD (801) 581-5619.

October 3—**The Complexities of Interpreting CT Scans in Lumbar Disc Disease** (Sponsors: Western Neurological Associates/American College of Radiology). Salt Lake City. Saturday. Hilton Hotel. 6 hrs. Fee: $100. Contact: Linda June Krueger, 1151 East 3900 South, #150, Salt Lake City, UT 84117. (801) 262-3441.

October 9—**Topics in Pharmacology—Regional Joint ACP-ASIM Meeting** (Sponsors: University of Utah/American College of Physicians). Salt Lake City. Friday. Hilton Hotel. Hrs. to be announced. Fee: $20. Contact: Gregory A. Schwitzer, MD (801) 581-7818.

October 16-27—**Western Mediterranean Air/Sea Cruise and Medical Seminar** (Sponsors: Washington University School of Medicine (St. Louis)/Utah State Medical Association). Portugal, Morocco, Gibraltar, Spain, Italy, France. Friday-Tuesday. 27 hrs. Fee: $250 (Medical Seminar Registration Only). Contact: Maxcine Fry (801) 355-7477.

November 2-7—**Training and Certification of Pulmonary Function Testing** (Sponsor: University of Utah). Location to be announced. Monday-Saturday. 17.5 hrs. Fee: To be announced. Contact: P. Lockey, MD (801) 581-3455.

November 6—**Renal/Pulmonary Syndrome — Postgraduate Course** (Sponsor: LDS Hospital). Salt Lake City. Friday. Hotel Utah. Hrs. and Fee to be announced. Contact: C. DuWayne Schmidt, MD (801) 350-1813.

November 13-14—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Tri-Arc Travelodge. 17 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 581-7617.

December 4-5—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 17 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

December 10-12—**Dilemmas of Ethics and Health: Informed Consent Conference** (Sponsor: University of Utah). Park City. Thursday-Saturday. 11 hrs. Fee: $175. Contact: Albertha Western (801) 581-6233.

January 3-9—**9th Annual Symposium on Clinical Echocardiography** (Sponsors: American College of Cardiology/University of Utah). Snowbird. Sunday-Saturday. 22.5 hrs. Fee: $200-$300. Contact: A. D. Hagen, MD (801) 350-1185.

January 11-23—**Perinatal/Neonatal Administrative Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Monday-Saturday. Salt Lake Marriott. 58 hrs. Fee: $100-$300. Contact: Jean Thornton, RN (801) 581-7085.

January 13-14—**Diabetes Update** (Sponsor: Regional Medical Education Center/VA Hospital). Salt Lake City. Thursday-Friday. Hotel Utah. 12 hrs. Fee: To be announced. Contact: Nancy Harrison (801) 582-1565, ext. 1100.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 18 hrs. Fee: $245. Contact: Claire Turner (801) 581-7617.

January 29-30—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

February 8-11—**11th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 32 hrs. Fee: $250. Contact: Linda Twitchell (801) 581-8633.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Friday-Tuesday. Location: To be announced. 16 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 21-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Sunday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain Pediatric Society Annual Scientific Meeting** (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Wednesday-Thursday. Location: To be announced. 12 hrs. Fee: To be announced. Contact: John Carey, MD (801) 581-8943.

March 25-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Wednesday-Friday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

October 15—**Enhancing Clinical Skills in Counseling Lesbian and Gay Clients and Their Families.** Seattle. Thursday. University of Washington—HUB. Contact: Seattle Counseling Service, 1505 Broadway, Seattle, WA 98122. (206) 329-8737.

October 15—**Cancer Pain: Assessment and Intervention in Nursing Practice.** Seattle. Thursday. Stuart Auditorium, Fred Hutchinson Cancer Research Center. Contact: Sue Porter, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104. (206) 292-2468.

October 15-16—**Obstetrics for the 80's.** Everett. Thursday-Friday. Everett Community College. Contact: Sheri Lindquist, Medical Education Coordinator, Snohomish County Medical Education Board, PO Box 1147, Everett, WA 98206. (206) 258-6322.

October 16-17—**Psychiatry for the Nonpsychiatrist.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 16-18—**Cytology Continuing Education Workshop.** Anchorage, Alaska. Friday-Sunday. Contact: CME Harborview.

October 23-24—**Washington State Psychiatric Association, Seattle Chapter: The Borderline Syndrome.** Seattle. Friday, 6:00 pm-9:15 pm (Dinner Meeting); Saturday, 9:00 am-5:00 pm. University Tower Hotel. Contact: Marilyn Goebel, Program Secretary, 816 23rd Ave., Seattle, WA 98122. (206) 329-8105.

October 29-30—**Degenerative Joint Disease.** Seattle. Thursday-Friday. Park Hilton Hotel. Contact: Marilyn Carlson, Northwest Hospital, Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

October 30—**Annual Cancer Conference for Family Physicians.** Seattle. Friday. Providence Medical Center. Contact: Gene Hooyman, PhD, Cancer Control Program, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104. (206) 292-2648.

October 30—**New Therapeutic Options in GI and Hepatobiliary Disorders.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 7—**The Care of Aging Patients.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

November 7—**Medical Ethics.** Tacoma. Saturday. Contact: CME Pierce County.

November 18—**Cadaver Kidney Retrieval.** Seattle. Wednesday. Virginia Mason Medical Center. Contact: VMMC.

November 19-20—**Current Urological Practice.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

December 4—**Practical Pediatrics. Seattle.** Friday. Virginia Mason Medical Center. Contact: VMMC.

December 10-12—**Cytology Continuing Education Workshop.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: CME Harborview.

January 15—**Perspectives in Rheumatology and Clinical Immunology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 28-30—**Cytology Continuing Education Workshop.** Portland, OR. Thursday-Saturday. Contact: CME Harborview.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 5-6—**Case Studies in Internal Medicine.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1982—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 12-16, 1981, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1982—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 1-3, 1981, Copper King Inn, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: October 29-30, 1981, Portland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: 1982—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1982—date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Midwinter Seminar January 7-9, 1982, Teton Village, Jackson. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

March 1-2—**Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego, CA. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 15-17—**Cytology Continuing Education Workshop.** Billings, MT. Thursday-Saturday. Contact: CME Harborview.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

August 19-21—**Cytology Continuing Education Workshop.** Eugene, OR. Thursday-Saturday. Contact: CME Harborview.

September 16-18—**Cytology Continuing Education Workshop.** Jackson, WY. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

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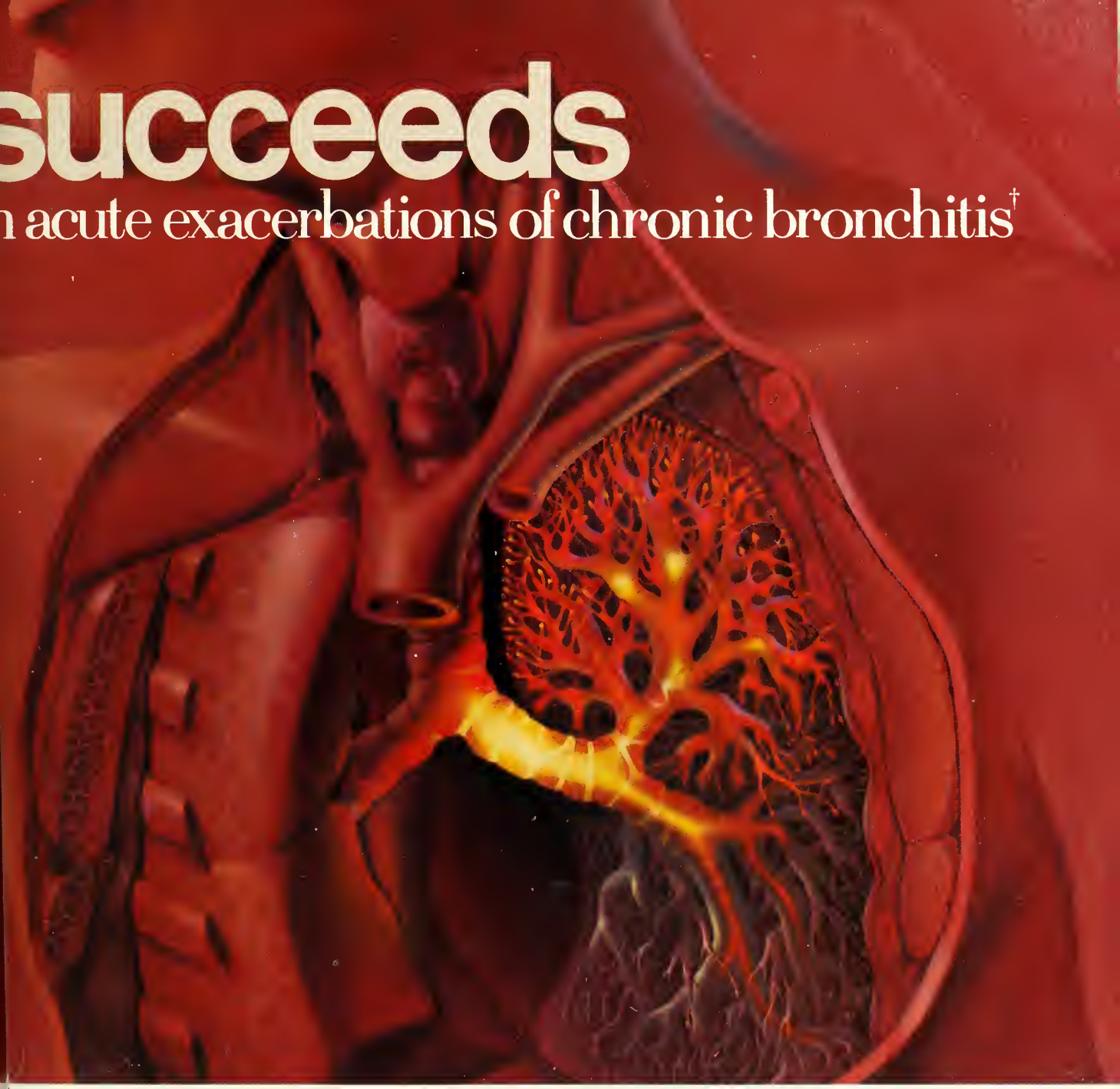

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Ru n RH, Swartz MH: *N Engl J*
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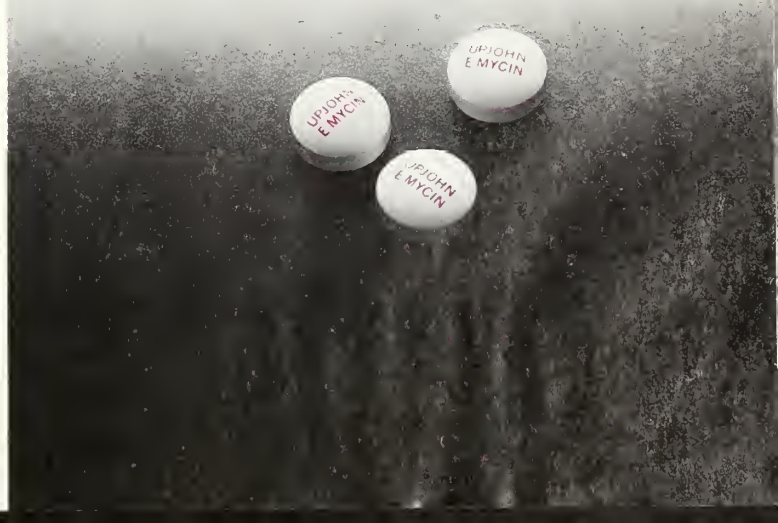

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379 *Cardiology Consultation* KENNETH F. HOSSACK, MD
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380 *Dermatology Consultation* JOHN E. OLERUD, MD, and GEORGE F. ODLAND, MD
Drs. Olerud and Odland are both from the Division of Dermatology, Department of Medicine.

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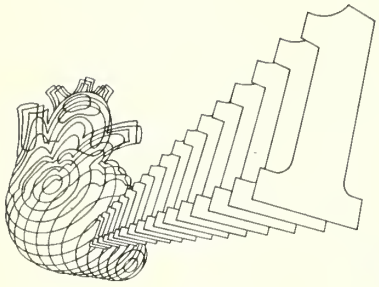
The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets
DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.
PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occur commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.
HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

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See following page for brief summary of prescribing information.

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Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistance may develop during treatment.
Streptococcus pneumoniae: Upper respiratory tract infections (eg, otitis media, pharyngitis) and lower respiratory tract infections (eg, pneumonia) of mild to moderate degree.
Mycoplasma pneumoniae (Eaton agent, PPLO): For respiratory infections due to this organism.
Treponema pallidum: An alternative treatment for penicillin-allergic patients.
Corynebacterium diphtheriae and *Corynebacterium minutissimum:* An adjunct to antitoxin, to prevent or treat carriers. In the treatment of erythrasma.
Entamoeba histolytica: Intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.
Listeria monocytogenes: Infections due to this organism.
Neisseria gonorrhoeae: In conjunction with erythromycin lactobionate injection in patients allergic to the penicillins. Patients should have a microscopic examination for *T. pallidum* (by immunofluorescence or darkfield).
Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity, in combination with sulfonamides. Not all strains are susceptible.
Bordetella pertussis: Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.
Legionnaires' disease: In vitro and limited clinical data suggest efficacy. Establish susceptibility of organisms to erythromycin.
Contraindication: Known hypersensitivity to erythromycin.
Warning: Safety for use in pregnancy has not been established.
Precautions: Erythromycin is principally excreted by the liver. Exercise caution in patients with impaired hepatic function. Hepatic dysfunction, with or without jaundice, has occurred with oral erythromycin products. Surgical procedures should be performed when indicated. Concurrent use with theophylline may potentiate theophylline toxicity. Theophylline dosage should therefore be reduced.
Adverse Reactions: The most frequent side effects are gastrointestinal, eg, abdominal cramping and discomfort, and are dose related. Nausea, vomiting, and diarrhea occur infrequently. During prolonged or repeated therapy, nonsusceptible bacteria or fungi may overgrow. The drug should then be discontinued and appropriate therapy instituted. Urticaria and other skin rashes have occurred. Serious allergic reactions, including anaphylaxis, have been reported.
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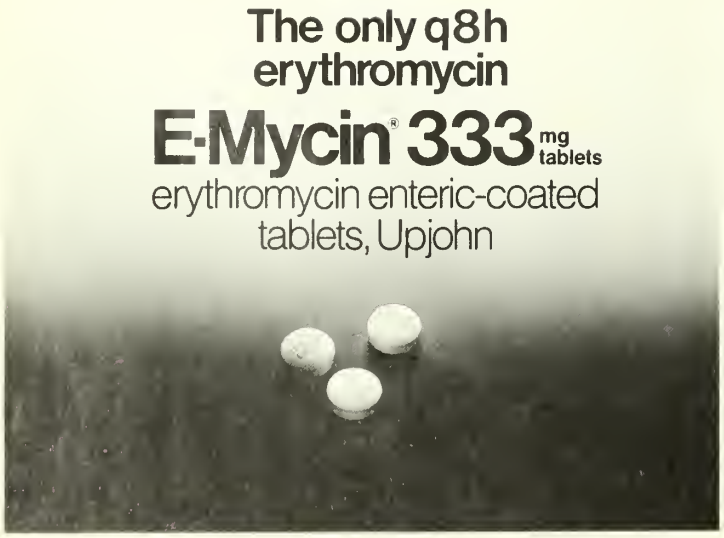

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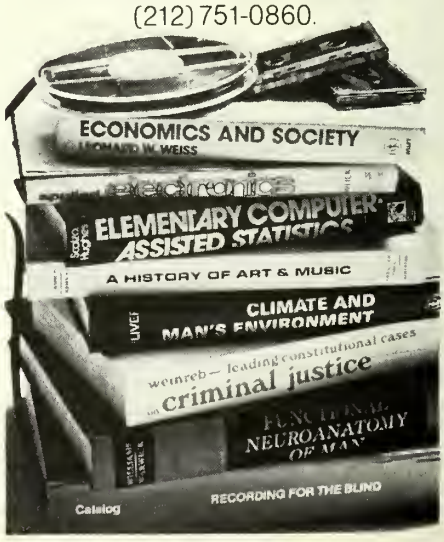

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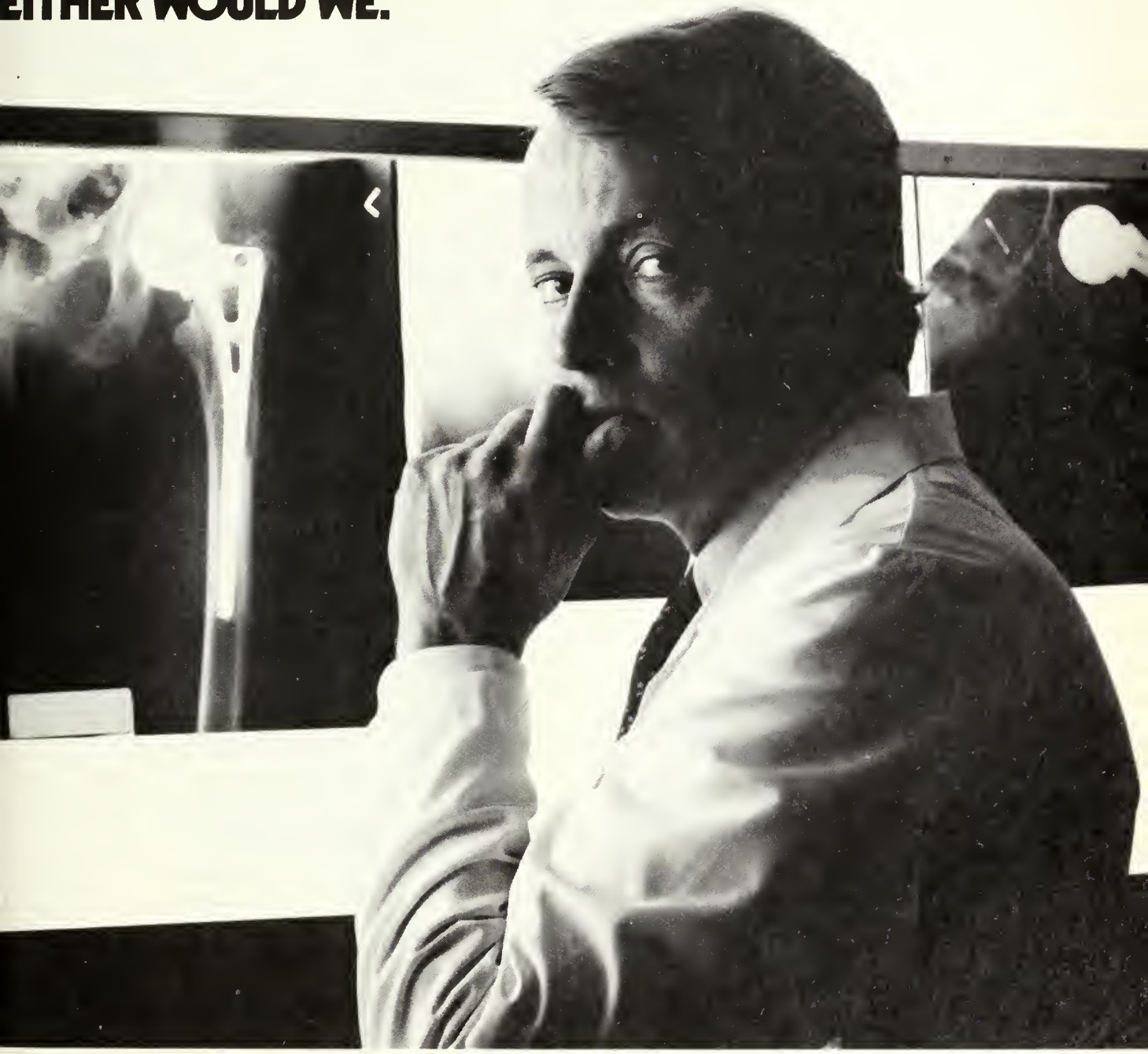

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ANESTHESIOLOGY

January 7-10—**Anesthesiology Update.** UCSD at Hotel del Coronado, Coronado. Thursday-Sunday.

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-18—**International Anesthesia Research Society—56th Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: International Anesthesia Research Soc., 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 17-21—**American Society of Regional Anesthesia.** Del Monte Hyatt, Monterey. Wednesday-Sunday. 16 hrs. $175. Contact: Gale Thompson, MD, ASRA, P.O. Box 11083, Richmond, VA 23230. (804) 358-0305.

April 3-10—**10th Obstetric Anesthesia Conference.** Dept. of Anesthesiology, Ohio State Univ. College of Medicine, at Sheraton Waikiki, Oahu, Hawaii. One week. 25 hrs. Contact: Dept. of Anesthesiology, c/o Bradford Travel, 1200 W. Henderson Rd., Columbus, OH 43220. (614) 457-9990 or (614) 421-8487 (OSU).

CANCER

December 16—**17th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

February 27-28—**Breast Cancer: Conservation Surgery and Radiation Therapy Now—17th Annual San Francisco Cancer Symposium.** West Coast Cancer Fndn.; Am. Cancer Soc., Calif. Div.; St. Mary's Hosp. and Med. Ctr. at Sheraton Fisherman's Wharf, San Francisco. Saturday-Sunday. 12 hrs. $115 before Jan. 1; $140, thereafter. Contact: West Coast Cancer Fndn., 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

EMERGENCY MEDICINE

November 23-24—**Advanced Cardiac Life Support.** Emergency Care Education Center at Queen Mary, Long Beach. Monday-Tuesday. 12 hrs. $130. Contact: ECEC, P.O. Box 9639, Marina Del Rey 90291. (213) 822-1312.

December 6-8—**American Society of Hospital-Based Emergency Air Medical Services—2nd Annual Conference.** UCSD at Hanalei Hotel, San Diego. Sunday-Tuesday. 8 hrs. $175.

December 7-10—**Postgraduate Institute for Emergency Room Physicians, Symposium IV.** UCSD at Vacation Village, San Diego. Monday-Thursday.

December 12—**Managing Pediatric Emergencies.** See Pediatrics, December 12.

December 14-18—**Postgraduate Institute for Emergency Room Physicians, Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs. $425.

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

When she can't manage, you can.

The sweats. The hot flushes. The distress and discomfort of atrophic vaginitis. The possibility of osteoporosis.* The menopause.

For many women, it's a time of confusion and frustration. Counseling can help her overcome these feelings. But counseling can't stop moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard bone loss*... the true signs of estrogen deficiency. And that's where she needs you most.

You're an expert at estrogen replacement. You know why it should be used. When it's best avoided. That it's not intended to treat nervous symptoms or depression associated with the menopause. That it can be very helpful in treating symptoms related to estrogen deficiency. You know how to cycle therapy. Determine dosage. Check for contraindications and possible complications. Follow-up. You know when therapy should begin, and when it deserves to end.

Most of all, you know your patient—and when she really needs the effective relief you can give her with PREMARIN.

When it comes to managing the estrogen-deficiency symptoms of the menopause, you've got what it takes.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

Prescribed with care by physicians who care.

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg/0.625 mg/1.25 mg/2.5 mg

Please see following page for Brief Summary of Prescribing Information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year[1-3] This risk was independent of the other known risk factors for endometrial cancer These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers The risk appears to depend on both duration of treatment[1] and on estrogen dose[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration,[3] it therefore appears prudent to utilize such a regimen Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)
2 Atrophic vaginitis
3 Kraurosis vulvae
4 Female hypogonadism
5 Female castration
6 Primary ovarian failure
7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8 Prostatic carcinoma—palliative therapy of advanced disease
9 Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions. 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, if has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression.[23,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen.

a Increased sulfobromophthalein retention
b Increased prothrombin and factors VII, VIII, IX, and X decreased antithrombin 3, increased norepinephrine-induced platelet aggregability
c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered
d Impaired glucose tolerance
e Decreased pregnanediol excretion
f Reduced response to metyrapone test
g Reduced serum folate concentration
h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives. breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate folerance; aggravation of porphyria, edema; changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily)

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e g. three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis

Female hypogonadism—2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression)—1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement—3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer—1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No. 865—Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866—Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867—Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100. No 868—Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

PHYSICIAN REFERENCES: 1 Ziel, H K., *et al.* N Engl J Med *293*:1167-1170, 1975 2 Smith, D C., *et al.* N. Engl J Med *293*:1164-1167, 1975 3 Mack, T M., *et al.* N Engl J Med *294*:1262-1267, 1976 4 Weiss, N S., *et al.* N Engl J Med *294*:1259-1262, 1976 5 Herbst, A L., *et al.* N Engl J Med *284*:878-881, 1971 6 Greenwald, P, *et al.* N Engl J Med *285*:390-392, 1971 7 Lanier, A, *et al.* Mayo Clin Proc *48*:793-799, 1973 8 Herbst, A, *et al.* Obstet Gynecol. *40*:287-298, 1972 9 Herbst, A, *et al.* Am J Obstet Gynecol *118*:607-615, 1974 10 Herbst, A., *et. al.* N Engl J Med *292*:334-339, 1975 11 Staff, A., *et al.* Obstet Gynecol *43*:118-128, 1974 12 Sherman, A I., *et al.* Obstet Gynecol *44*:531-545, 1974 13 Gal, I, *et al.*, Nature *216*:83, 1967 14 Levy, E P., *et al.* Lancet *1*:611, 1973 15. Nora, J., *et al.* Lancet *1*:941-942, 1973 16 Janerich, D T., *et al.* N Engl J Med *291*:697-700, 1974 17 Boston Collaborative Drug Surveillance Program N Engl J Med *290*:15-19, 1974 18 Hoover, R., *et al.* N Engl J. Med *295*:401-405, 1976. 19 Daniel, D G., *et al.* Lancet *2*:287-289, 1967. 20 The Veterans Administration Cooperative Urological Research Group: J. Urol *98*:516-522, 1967 21 Bailar, J C Lancet *2*:560, 1967 22 Blackard, C., *et al.* Cancer *26*:249-256, 1970 23 Royal College of General Practitioners: J R Coll Gen Pract *13*:267-279, 1967. 23a Royal College of General Practitioners. Oral Contraceptives and Health, New York, Pitman Corp., 1974 24 Inman, W H W, *et al.* Br Med J *2*:193-199, 1968 25. Vessey, M P, *et al* Br Med J *2*:651-657, 1969 26 Sartwell, P.E., *et al.* Am J. Epidemiol *90*:365-380, 1969 27. Collaborative Group for the Study of Stroke in Young Women N Engl J Med *288*:871-878, 1973 28 Collaborative Group for the Study of Stroke in Young Women J A M A *231*:718-722, 1975 29 Mann, J I., *et al* Br Med J *2*:245-248, 1975 30 Mann, J.I., *et al.*: Br. Med J *2*:241-245, 1975 31. Inman, W H W., *et al* Br Med J *2*:203-209, 1970 32 Stolley, P D., *et al.* Am J Epidemiol. *102*:197-208, 1975 33 Vessey, M.P., *et al.* Br. Med J. *3*:123-126, 1970 34 Greene, G R., *et al* Am J. Public Health *62*:680-685, 1972 35 Coronary Drug Project Research Group J A M A *214*:1303-1313, 1970 36 Mays, E T., *et al.*: J A M A *235*:730-732, 1976 37 Pfeffer, R I., *et al* Am J Epidemiol *103*:445-456, 1976

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(Continued from Page 19)

February 5-6—**Base Station Physician Symposium.** Calif. Chapter, Am. College of Emergency Physicians, at Ahwahnee Hotel, Yosemite. Friday-Saturday. 9 hrs. $125, ACEP members; $150, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., #240, Los Angeles 90045. (213) 776-1820.

February 7-12—**Winter Sports Injuries.** See Of Interest to All, February 7-12.

February 12-13—**Toxicologic and Infectious Disease Emergencies.** UCLA. Friday-Saturday.

February 28-March 5—**Emergency Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 7-10—**Sports Injuries Update.** UCD at Hyatt, Lake Tahoe. Sunday-Wednesday.

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

April 10-17—**Pediatric Emergencies.** UCSD at Kauai, Hawaii. One week. 21 hrs. $325.

April 24-May 2—**Emergency Medicine.** USC at Hawaii. One week. 25 hrs. $425.

MEDICINE

November 16-20—**First Mexican-American Congress of Allergy and Clinical Immunology.** Am. College of Allergists, Sociedad Mexicana de Allergia E Immunologia, Autonoma Univ. of Baja and UCSD at San Diego (16-18) and Tijuana (19-20). Monday-Friday. 21 hrs. $175 before Sept. 15; $200, thereafter. Contact: Robert N. Hamburger, MD, Immunology and Allergy Div., UCSD (M-009D), La Jolla 92093.

November 24—**Diagnosis and Treatment of Life-Threatening Infections.** UCD at Red Lion Motor Inn, Sacramento. Tuesday.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. 10 hrs. $125. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

December 4-5—**Cardiac Ischemia and Arrhythmias—Current Concepts for Diagnosis and Treatment.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 4-6—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8646.

December 5—**Cardiology for the Primary Care Physician I: Basic Electrocardiography.** PMC. Saturday. 6 hrs. $95.

December 5-10—**American Academy of Dermatology.** San Francisco. Saturday-Thursday. Contact: Cheryl Nordstedt, Dir., Meetings and Conventions, AAD, 820 Davis St., Evanston, IL 60201. (312) 869-3954.

December 9—**Hypertension.** LLU. Wednesday. 4 hrs.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** See Surgery, December 10-13.

December 11-13—**Cardiology for the Primary Care Physician.** UCD. Friday-Sunday.

December 12—**Clinics in Medicine—Endocrinology.** PMC. Saturday. 3 hrs. $40.

January-March—**Endocrinology for the Practicing Internist.** UCLA. Wednesday evenings.

January 8-15—**6th Annual Echocardiography Conference.** Honolulu Medical Group Research and Education Fndn. at Kauai Surf Resort, Kauai. One week. 32 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

January 9-15—**Gastrointestinal and Hepatic Diseases.** Honolulu Medical Group Research and Education Fndn. at Hyatt Regency, Maui. Saturday-Friday. 21 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9-16—**Endocrinology and Metabolism.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 13—**Rheumatology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 16-23—**Nephrology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $425.

January 20-23—**Conference on Nephrology and Hypertension.** UCSD at Hilton, San Diego. Wednesday-Saturday.

January 27-29—**Echocardiography: An Introductory Course for the Practicing Physician.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2-6—**What Is Ahead in Lung Diseases for the 80's.** USC at Death Valley. Tuesday-Saturday.

February 3-5—**Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 6—**Clinics in Medicine—Rheumatology.** PMC. Saturday. 3 hrs. $40.

February 12-13—**Rheumatology Medicine.** UCD. Friday-Saturday.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 18-20—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 18-20—**Controversies and Problem Solving With Endoscopy—An Update.** So. Calif. Society for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 18 hrs. Contact: Dr. Albert Dreskin, 13652 Cantara St., Panorama City 91402.

February 20-27—**Cardiology.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Sunday-Tuesday.

February 25-28—**Federation of the Western Societies of Neurological Science.** Hotel del Coronado, Coronado. Thursday-Sunday. 15 hrs. Contact: Renee Kaseff, 525 Hurlingham Ave., San Mateo 94402. (415) 344-9082.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

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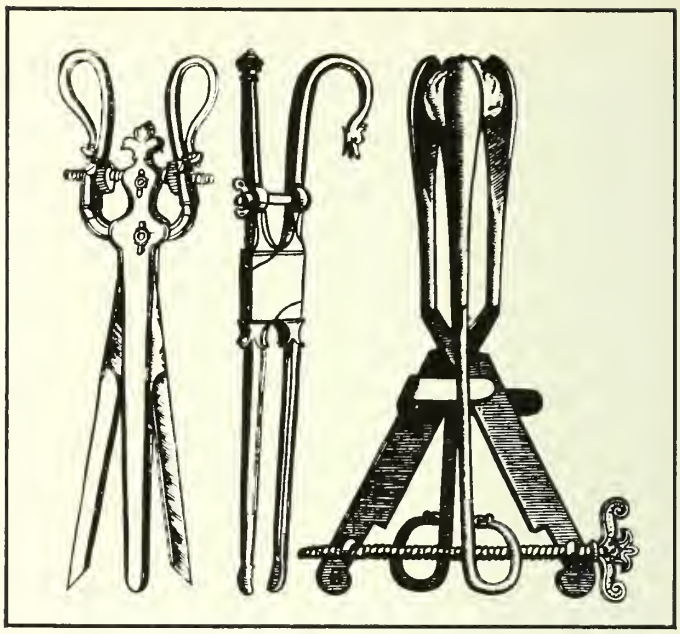
Perspectives on Progress



Hans Gersdorff, Ambroise Pare; Bibliothéque de Genéve.

Genetics in Obstetrics
New Insulins
Electrosurgery in the 80's
Ultrasonography of Vitreo-Retinal Pathology
Chemotherapy of Neoplasms of the Central Nervous System
Tumor-Seeking Radiopharmaceuticals
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Female Sterilization and Reversal
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Psychological Reactions to Breast Reconstruction
Chlamydial Trachomatis
Cooperative Parenting — Custody Issues
Digital Neuroradiology
Installation of Medical Computers
Medical-Social Treatment for Alcoholism

These are just a few of the topics to be discussed at
California Medical Association's 111th Annual Session, March 12–17, 1982 at the Disneyland Hotel, Anaheim

Other highlights. . .
- Watch CMA policy being made at the House of Delegates meetings
- Join in CMA's Family Fun Day at Disneyland on Sunday, March 14, 1982
- Learn about medical and health-related advances — visit the scientific and technical exhibits

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Address: _____

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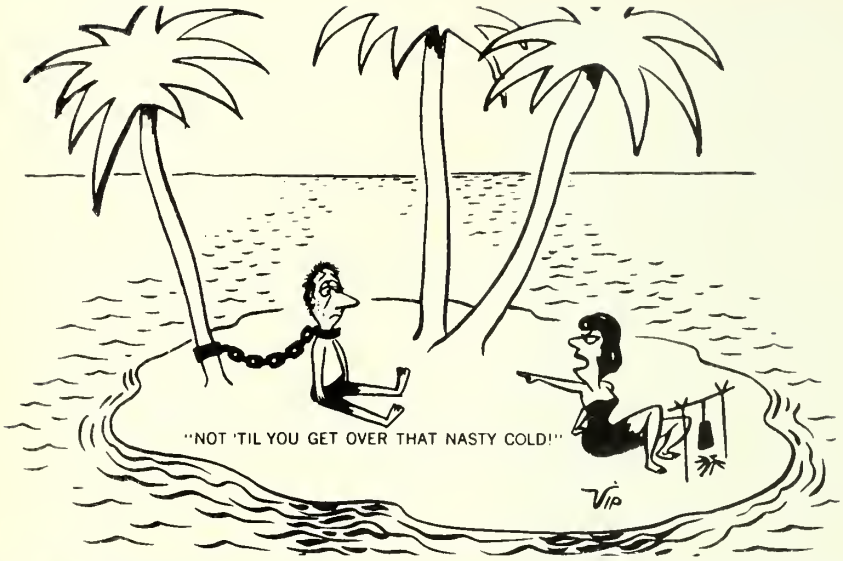

Citra® Forte Syrup stops stubborn coughs

... and with an Rx for CITRA® FORTE Capsules you can provide the additional benefits of helping your patients "feel well" for the duration of their colds—free of most cold symptoms.

BOYLE & COMPANY
Other Ethically Promoted Products

- Citra Capsules ... Antihistaminic/Decongestant/Analgesic for cold symptoms relief
- Digolase ... Digestive enzymes
- Glytinic Tablets and Liquid ... Iron plus aminoacetic acid for iron deficiency anemia
- Triva Douche Powder ... Treats all three types of vaginitis
- Rx • Triva Jel ... Provides continuous action
- Rx • Triva Combination ... Jel and Powder kit

CITRA® FORTE SYRUP

Each 5cc contains:

Hydrocodone Bitartrate	5 mg
(WARNING: May be habit forming)	
Ascorbic Acid	30 mg
Pheniramine Maleate	2.5 mg
Pyrilamine Maleate	3.33 mg
Potassium Citrate	150 mg

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.

CITRA® FORTE CAPSULES

Hydrocodone Bitartrate	5 mg.
(WARNING: May be habit forming)	
Ascorbic Acid	50 mg
Pheniramine Maleate	6.25 mg
Pyrilamine Maleate	8.33 mg.
Chlorpheniramine Maleate	1 mg
Phenylephrine HCl	10 mg.
Salicylamide	227 mg
Caffeine Alkaloid	30 mg.
Acetophenetidin	120 mg

PRECAUTIONS: Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients. CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.
WARNING: This preparation may damage the kidneys when used in large amounts or for a long period of time. Use with caution in greater than recommended dose or regularly for longer than 10 days (Acetophenetidin).

Boyle & Company/
Pharmaceuticals
13260 Moore Street,
Cerritos Ca 90701

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(Continued from Page 16)

PHYSICIANS WANTED

INTERNIST and GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guaranteed with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 E. 4th No, Logan, UT 84321.

PULMONARY, ALLERGY, and INFECTIOUS DISEASE subspecialists wanted to join a well-established pulmonary and infectious disease medical group in Northern California. Competitive salary and fringe benefits. Send CV to Box AIM, 6226, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTITIONERS NEEDED to practice with 280-man multispecialty group. Board certified or eligible. Salary negotiable. Excellent fringe benefits. Contact: James O. Farley, MD, Permanente Medical Group, P.O. Box 254999, Sacramento, CA 95825 or call collect (916) 486-5103. An Equal Opportunity Employer.

ORTHOPEDIC SURGEON—for busy general practice in outstanding Northern California suburban city, located 30 miles from San Francisco. Multiple recreational and educational opportunities available. Contact: Joel G. Goldman, MD, Permanente Medical Group, 1425 South Main, Walnut Creek, CA 94596; (415) 943-2633.

GASTROENTEROLOGIST, BE/BC to join 14 DR multispecialty group located in the Pacific NW between Seattle and Vancouver, BC. Competitive salary and fringe benefit program. Contact Shane Spray, 1400 E. Kincaid, Mt. Vernon, WA 98273; Phone (206) 428-2524.

CALIFORNIA/FAMILY PRACTICE: Opportunity to share growing young general practice with two board certified FP's. New hospital. Growing community Central California. Possible UCSF Medical School affiliation. 1½-hour drive to 3 national parks. Reply Box 6244, Western Journal of Medicine, 731 Market St., San Francisco 94103.

FAMILY PHYSICIAN—Indian Health Clinic half time position. Located in beautiful area one hour north of San Francisco with teaching hospital nearby. Competitive salary, excellent benefits. Contact SCIHP, Box 11126, Santa Rosa, California 95406; (707) 544-4056.

EXPANDING BARIATRICS PRACTICE—University type needs additional associate. Orange County. $2,000/month for 1-day week. Profit sharing with equity participation after 1 year. (714) 851-9354 contact Alan Helfman.

GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

GENERAL SURGEON
Pacific Northwest

Immediate practice opportunity adjacent to modern 147 bed hospital serving 60,000. Enjoy a relaxed semi-rural recreation area of the Washington coast. No smog or traffic congestion. Less than 2 hours by freeway from the Seattle metro area. Initial Investment flexible. Contact Jim Washam, Habor Medical Surgical Center, Box 482, Aberdeen, WA 98520 or call COLLECT (206) 533-0450. EOE.

PHYSICIANS WANTED

CARDIOLOGIST—SAN DIEGO AREA: Board Certified or eligible to join active, well established 10 physician multisubspecialty Internal Medicine Group. Clinical, Non-Invasive, Swan-Ganz, Temporary Pacemaker skills required. Salary plus bonus first year. Full partnership starting second year. Choice southern California location. Reply with CV to Box 6245, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GOLD COUNTRY, NORTHERN CALIFORNIA—On Lake Don Pedro. Will build to suit custom medical office (general practice) with residence. Ideal site in growing retirement/vacation area; 400,000 visitors/year. Emergency medical facilities nearby. Dave Copeland, 1794 E. Williams Street, San Jose, CA 95116; (408) 923-2931.

CALIFORNIA: Inquiries invited from career emergency physicians with PG training in emergency medicine or pertinent specialty or equivalent experience. Pre-paid multispecialty group. California license required. Contact: Peter Lau, MD, Permanente Medical Group, P.O. Box 254999, Sacramento, CA 95825; An Equal Opportunity Employer.

OLYMPIA, WASHINGTON: New clinic needs second physician who is Board Certified or eligible Family Practice and interested in OB. Call is shared with another group. Write: John Armentrout, MD, 2404 Heritage Ct. SW, Olympia, WA 98502.

SANTA BARBARA, CALIFORNIA: Immediate opening for Medical Oncologist/Hematologist to join a one physician Oncologist/Hematologist Department in a progressive multi-specialty clinic of 60 physicians. Excellent benefit package. Must be board eligible/certified. Send CV to: Administration, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102.

CARDIOLOGIST, GASTROENTEROLOGIST, AND RHEUMATOLOGIST—23 member multispecialty medical group seeks 3 full-time, board eligible/certified specialists. Excellent opportunities. Attractive compensation and benefits. Start date negotiable. Send résumé to Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd., Los Angeles, CA 90004; (213) 386-8440.

IMMEDIATE CARE PHYSICIAN—TO JOIN LITTLETON CLINIC, P.C., a 22 physician multi-specialty group located 7 miles south of Denver. The position requires 4½ days per week, 8:00 a.m.-5:00 p.m.; with salary plus productivity incentive; an excellent fringe benefits package; and an opportunity to enter the corporation the 2nd year. The successful applicant will have experience in minor surgery, fracture care, and Int. Med. Send CV to Richard L. Good, MD, Littleton Clinic, P.C., 1950 W. Littleton Blvd., Littleton, CO 80120.

(Continued on Page 33)

WA STATE
Position Opportunities

Aberdeen, Washington, a coastal community surrounded by mountains, rivers and ocean beaches is the health care center for a population base of 60,000.

A new clinic adjacent to a modern 147 bed hospital has space for the following specialist.

- ENT
- GENERAL SURGEON
- INTERNIST
- FAMILY PRACTITIONER

This is an Immediate opportunity with flexible initial investment. Contact Jim Washam, Habor Medical Surgical Center, Box 482, Aberdeen, WA 98520 or call COLLECT (206) 533-0450. EOE

M.J. Hall & Co., Inc.
Announces a NEW umbrella program to protect physicians and surgeons against malpractice and other catastrophe liability.

WRITTEN THROUGH
NORTH STAR EXCESS INSURANCE
CORPORATION

Available to physicians and surgeons who are members of their local Medical Societies, with the exception of those physicians and surgeons who have their practices in either Alameda, Los Angeles or San Francisco counties.

If you are not doing business with a licensed broker in your area, we would like to provide you with a number of names.

MANAGING GENERAL AGENTS
SURPLUS LINES & EXCESS BROKERS
LLOYD'S OF LONDON CORRESPONDENTS
M.J. HALL & COMPANY, INC.

M.J. HALL & CO., INC.
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P.O. Box 192,
Stockton, CA 95202
(209) 948-8108
Telex: 359-410

New from Janssen Pharmaceutica: Introducing a promising new approach to coccidioidomycosis therapy

NIZORAL™ TABLETS (ketoconazole)

New:

the first and only orally effective, broad-spectrum antifungal agent.

NIZORAL (ketoconazole) is clinically effective against the major yeast and fungal pathogens. For *C. immitis,* the average MIC is less than 1 μg/ml. Absorption of ketoconazole is rapid; mean peak plasma levels of approximately 3.5 μg/ml are reached within 1-2 hours following a single 200 mg tablet. Development of resistance to NIZORAL has not yet been reported.

Effective:

"...a promising new drug for treatment of coccidioidomycosis."[1]

Clinical studies employing 200 to 400 mg NIZORAL per day have shown a combined response rate* of 35% after 26 (median) weeks of therapy; (at this point, however, 69% of patients were still being treated). Most patients were severe and chronic cases, either failures on or intolerant to amphotericin B.[2] (Recommended minimum treatment is 180 days.)

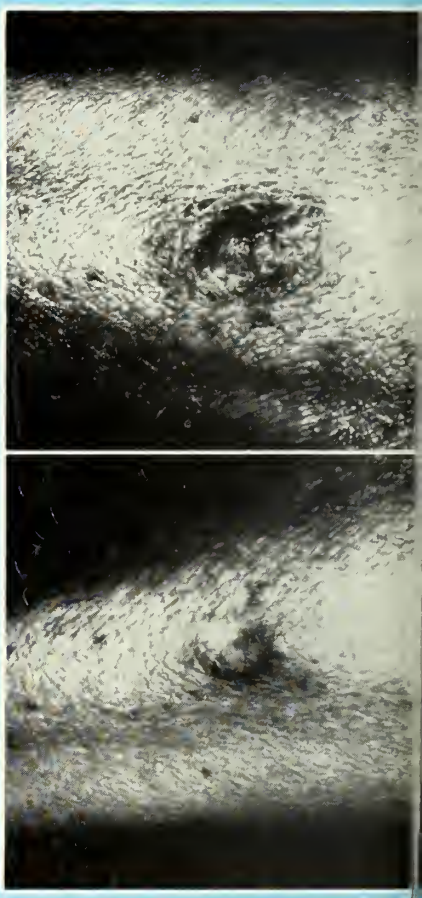
Safe:

"...can be safely administered for prolonged periods..."[3]

Freedom from long-term toxicity permits use of extended therapeutic courses of NIZORAL, when indicated, and provides an extra margin of safety in presumptive antifungal therapy. Long-term administration has revealed no organ toxicity and no consistent changes in important hematological or biochemical values. Infrequent, transient increases in serum liver enzymes have been seen. Adverse reactions were generally minor and only rarely required withdrawal of therapy.

Convenient:

once-a-day oral regimen fosters compliance...facilitates use both in and out of the hospital.



Top: Cutaneous lesion, disseminated coccidioidomycosis, before therapy.

Bottom: Lesion markedly resolved after oral NIZORAL therapy; photographed at 18 months

*Includes cases in remission or markedly improved (no evidence of active disease); both mycological and clinical criteria were considered in measuring overall response.

For further information on NIZORAL write: Professional Services, Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903.

See the facing page for Complete Prescribing Information.

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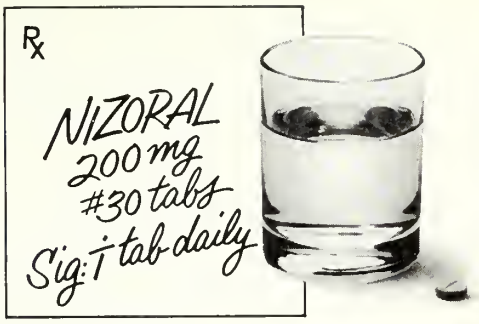
JPI-209

JANSSEN PHARMACEUTICA

NEW orally effective

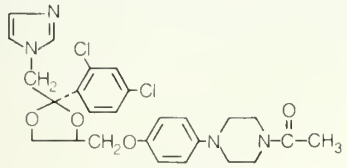
NIZORAL™ TABLETS (ketoconazole)

One tablet a day provides broad-spectrum antimycotic efficacy



DESCRIPTION

NIZORAL™ (ketoconazole) is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole. Ketoconazole is *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:



NIZORAL™ is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44

CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately 3.5 μg/ml are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL™ is converted into several inactive metabolites. The major identified metabolic pathways are: oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99%, mainly to the albumin fraction. Only a negligible proportion of NIZORAL™ reaches the cerebral spinal fluid. NIZORAL™ is a weak dibasic agent and thus requires acidity for dissolution and absorption.

NIZORAL™ is active against clinical infections with *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Phialophora* spp. Development of resistance to NIZORAL™ has not yet been reported.

The following preclinical data are available, however, their clinical significance is unknown. NIZORAL™ is active *in vitro* against dermatophytes, dimorphic fungi, eumycetes, yeasts, actinomycetes, phycomycetes and various other fungi. In animal models, activity has been demonstrated against *Candida* spp., dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Coccidioides immitis*, and *Cryptococcus neoformans*.

Mode of Action: *In vitro* studies suggest that NIZORAL™ impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. Tests in animals suggest this mechanism is not important in mammalian cells.

INDICATIONS AND USAGE

NIZORAL™ is indicated for the treatment of the following fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL™ should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

For the initial diagnosis, the infective organism should be identified; however, therapy may be initiated prior to obtaining laboratory results.

CONTRAINDICATIONS

NIZORAL™ is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

General: In four subjects with drug-induced achlorhydria, a marked reduction in NIZORAL™ absorption was observed. NIZORAL™ requires acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least two hours after NIZORAL™ administration. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a glass or plastic straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Drug Interactions: There is no evidence for clinically significant interaction with oral anticoagulant or oral hypoglycemic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of NIZORAL™ as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames' *Salmonella* microsomal activator assay was also negative.

Pregnancy: Teratogenic effects: *Pregnancy Category C*. NIZORAL™ has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day, (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

Nonteratogenic effects: NIZORAL™ has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered NIZORAL™ during the third trimester of gestation. This occurred when NIZORAL™ was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of NIZORAL™ during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD_{50} of NIZORAL™ given by gavage to the female rat is 166 mg/kg, whereas in the male rat the oral LD_{50} is 287 mg/kg.

Nursing Mothers: Since NIZORAL™ is probably excreted in the milk, mothers who are under NIZORAL™ treatment should not breast-feed the child.

Pediatric Use: Safety in children under two years of age has been documented in a limited number of cases.

ADVERSE REACTIONS

NIZORAL™ is usually well tolerated. Most adverse reactions reported have been mild and transient and have only rarely required withdrawal of therapy.

The most frequent adverse reactions were nausea and/or vomiting, which occurred in approximately 3% of patients. Abdominal pain was reported in approximately 1.2% of patients; pruritus in approximately 1.5% of patients. The following have been reported in less than 1% of patients: headache, dizziness, somnolence, fever and chills, photophobia, and diarrhea. Infrequent, transient increases in serum liver enzymes have been seen.

OVERDOSAGE

In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting dose of NIZORAL™ is a single daily administration of 200 mg (one tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of NIZORAL™ may be increased to 400 mg (two tablets) once daily.

Children:

Children weighing 20 kg or less: . . . . . 50 mg (¼ tablet) once daily
Children weighing 20-40 kg: . . . . . 100 mg (½ tablet) once daily
Children weighing over 40 kg . . . . . 200 mg (1 tablet) once daily

Generally, treatment should be continued until all clinical and laboratory tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is one or two weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is six months.

HOW SUPPLIED

NIZORAL™ is available as white, scored tablets containing 200 mg of ketoconazole debossed "JANSSEN." They are supplied in bottles of 60 tablets.

U.S. Patent Pending — May 1981
NDC 50458-220-06 (60 tablets)

Manufactured by:
Janssen Pharmaceutica n.v.
B-2340 Beerse, Belgium

For:
Janssen Pharmaceutica Inc.
New Brunswick, New Jersey 08903 USA

References:

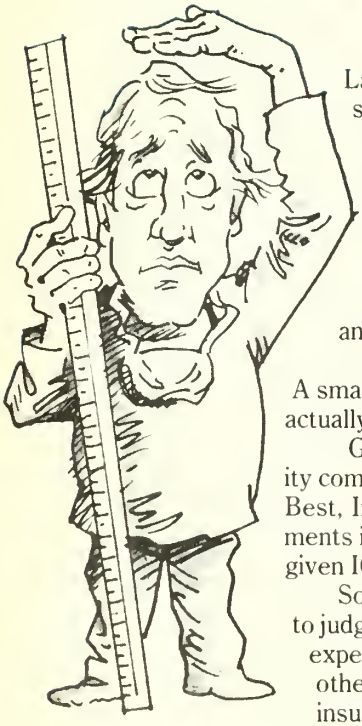
1. Brass C, Galgiani JN, Campbell SC, et al: Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. *Reviews of Infectious Diseases* 2 (4): 656-660, 1980. **2.** Data on file, Janssen Pharmaceutica. **3.** Graybill JR, Lundberg D, Donovan W, et al: Treatment of coccidioidomycosis with ketoconazole: Clinical and laboratory studies of 18 patients. *Reviews of Infectious Diseases* 2 (4): 661-673, 1980.

Committed to research...
because so much remains to be done.

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903

MYTHS, HAL
FINALLY TH
MALPRACT



Lately, a great deal of misinformation has been circulated on the subject of professional liability insurance. At ICA we think it's time you got the facts.

JUDGING AN INSURANCE COMPANY BY ITS SIZE IS LIKE CHOOSING A DOCTOR BY HIS HEIGHT.

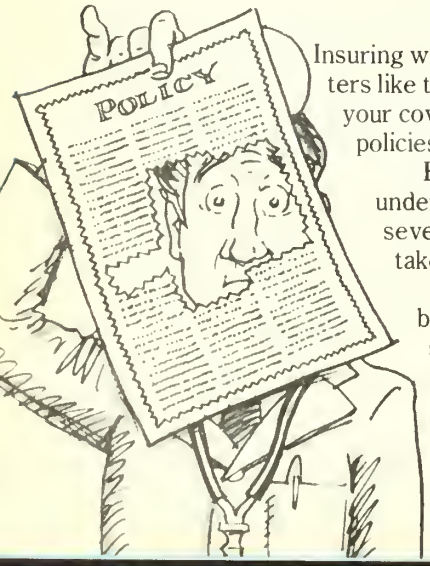
Big is not automatically better. Contrary to what large insurance companies would like you to believe, financial stability, experience, and quality coverage are not related to size.

First, greater size does not assure stability. A smaller company's ratios reflecting stability may actually be more favorable than a large company's.

Generally, confirmation of a company's stability comes from the state regulatory boards and A. M. Best, Inc. ratings. ICA has met the rigid state requirements in every market where we write and "Bests" has given ICA a very good policyholders rating.

So don't be fooled by big boasts. There are better ways to judge a company. Look for experience. But make sure it's experience that counts. A huge company's years devoted to other lines of insurance won't help. Medical malpractice insurance is totally different.

At ICA we know. Professional liability is our field. Over the years we have consistently offered the strongest possible benefits combined with the highest standards for the professional handling of claims.



HOW A TORNADO IN TULSA CAN HELP SEND YOUR MALPRACTICE RATES THROUGH THE ROOF.

Insuring with a large, multiline company can have its hazards. Major disasters like tornadoes, fires, or earthquakes may effect the overall costs of your coverage because when a multiline company has a loss, all of their policies may help pay.

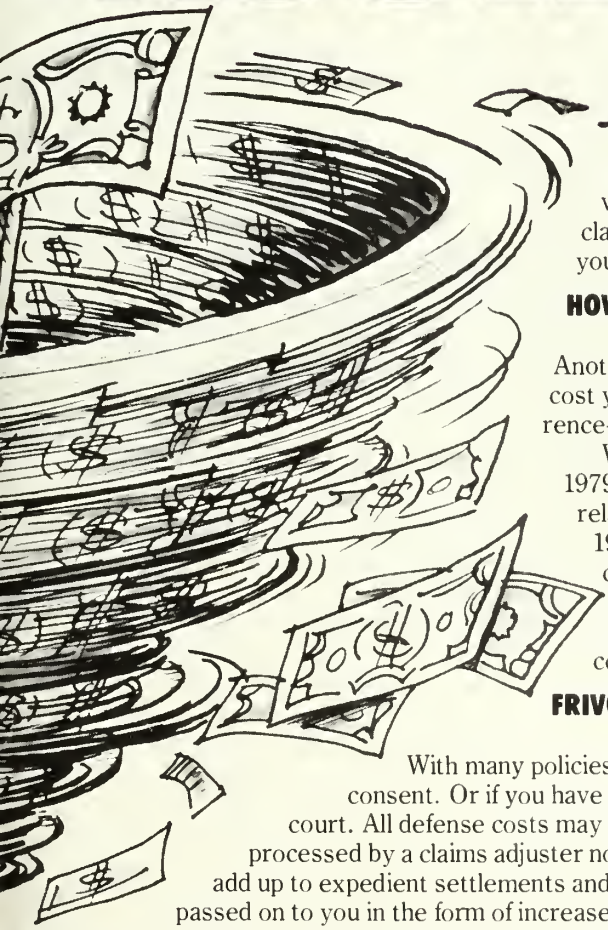
Higher rates happen another way, too. Many companies greatly underestimated the cost of writing malpractice insurance in the early seventies. If you're insured with them today, you're paying for their mistake with higher rates as they try to catch up.

At ICA our rates reflect our true costs. We even set rates state by state. So you don't pay for another state's higher risk history. Our strong handling of frivolous claims also helps keep costs down. But don't judge a policy by rates alone.

HOW RENEWING THE VERY SAME POLICY COULD BE GIVING YOU VERY DIFFERENT BENEFITS.

Do your rates stay the same while your benefits shrink? At some companies one or two word changes each year can keep a policy profitable

TRUTHS, AND ACTS ABOUT INSURANCE.



for them but can leave you increasingly vulnerable. Like changing the consent clause, so a claim can be settled without your consent.

HOW THE FIRST DAY OF RETIREMENT COULD COST YOU $100,000.

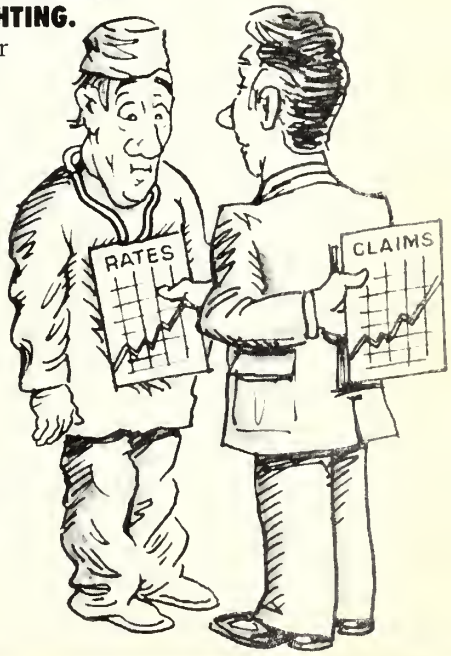
Another change companies make that can cost you plenty is to switch your 'occurrence-form' policy to a 'claims-made' one.

With an 'occurrence-form' policy in say 1979, you're always insured for claims related to that year. Even if a claim is made in 1999. With a 'claims-made' policy coverage expires completely if you fail to renew. To keep coverage after retirement you may have to pay an exorbitant fee set by your company and years of inflation. And the limited coverage it buys you is all you have to cover your entire career.

FRIVOLOUS CLAIMS AND HOW SOME COMPANIES MAKE A POLICY OF NOT FIGHTING.

With many policies, a claim can be settled without your consent. Or if you have a say, there's a penalty for going to court. All defense costs may not be paid and your case may be processed by a claims adjuster not an attorney. These features can add up to expedient settlements and the resulting costs are easily passed on to you in the form of increased premiums.

At ICA policies are designed to protect you. Tough, professional handling of claims guards your reputation and helps keep costs down. Ours and yours. At ICA we can offer what others can not. Because we are a doctor and attorney owned company that specializes solely in professional liability insurance. Our background and dedication to this one field have allowed us to both know its needs and know how to meet them.



For more facts, contact: Insurance Corporation of America, ICA Center, 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2615. In Texas 1-800-392-9702. (Check for availability in your state.)

ICA **PROFESSIONAL LIABILITY INSURANCE**

WE'RE THE SPECIALIST IN THE FIELD

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently, both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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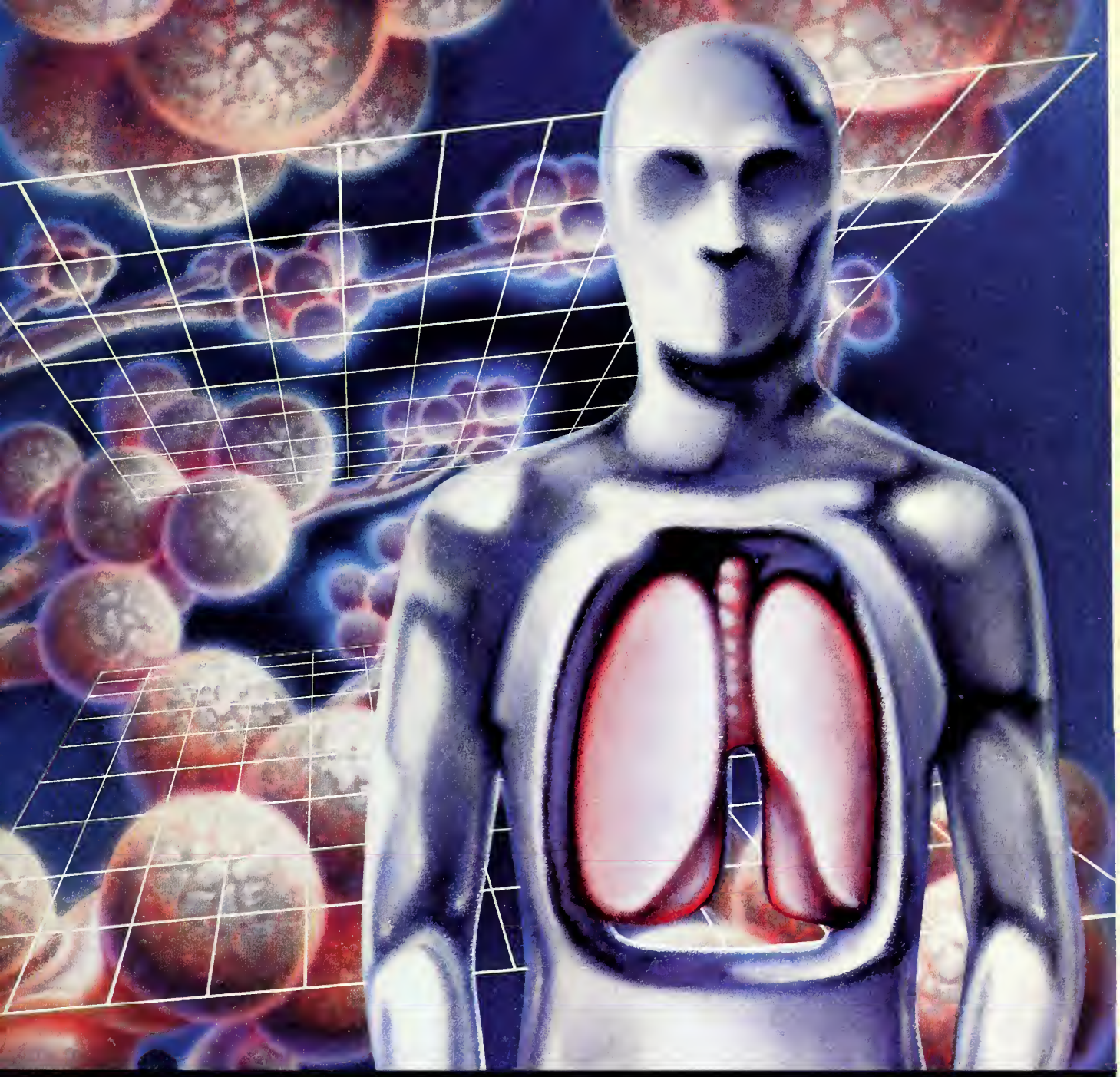


No inhaler dilates bronchioles better. Or faster. Or longer. Or more safely. Or more selectively.

That's why the aerosol bronchodilator known internationally as salbutamol* Ventolin® Inhaler is the most widely prescribed inhaler in the world.

Ventolin®
albuterol
Glaxo **Inhaler**

unsurpassed in the world of bronchodilation

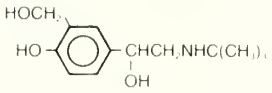
*Official U.S. designation albuterol Ventolin® Inhaler

The bronchodilator with an unsurpassed clinical profile

Ventolin® albuterol Glaxo Inhaler

the most widely-prescribed inhaler in the world

DESCRIPTION The active component of VENTOLIN Inhaler is albuterol (α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective beta$_2$-adrenergic bronchodilator having the chemical structure



Albuterol is the official generic name in the United States. The international generic name for the drug is salbutamol. The molecular weight of albuterol is 239.3.

VENTOLIN Inhaler is a metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers from the mouthpiece 90 mcg of albuterol. Each canister provides at least 200 inhalations.

CLINICAL PHARMACOLOGY The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3', 5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. By virtue of its relatively selective action on beta$_2$-adrenoceptors, albuterol relaxes smooth muscle of the bronchi, uterus, and vascular supply to skeletal muscle, but may have less cardiac stimulant effects than does isoproterenol.

Albuterol is longer acting than isoproterenol by any route of administration in most patients because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase.

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses. Studies undertaken with four subjects administered tritiated albuterol, resulted in maximum plasma concentrations occurring within two to four hours. Due to the sensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72 percent of the inhaled dose is excreted within 24 hours in the urine, and consists of 28 percent of unchanged drug and 44 percent as metabolite.

Results of animal studies show that albuterol does not pass the blood-brain barrier.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that albuterol is $\frac{1}{2}$ to $\frac{1}{4}$ as active as isoproterenol in producing increases in heart rate. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

INDICATIONS AND USAGE VENTOLIN Inhaler is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease.

In controlled clinical trials the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximal midexpiratory flow rate (MMEF) and FEV$_1$. MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following 2 inhalations of albuterol and that clinically significant improvement generally continues for 3 to 4 hours in most patients. In clinical trials, some patients with asthma showed a therapeutic response (defined by maintaining FEV$_1$ values 15 percent or more above base line) which was still apparent at 6 hours. Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials.

CONTRAINDICATIONS VENTOLIN Inhaler is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS As with other adrenergic aerosols, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

The contents of VENTOLIN Inhaler are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

PRECAUTIONS Although it has less effect on the cardiovascular system than isoproterenol at recommended dosages, albuterol is a sympathomimetic amine and as such should be used with caution in patients with cardiovascular disorders, including coronary insufficiency and hypertension, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes and ketoacidosis. The relevance of this observation to the use of VENTOLIN Inhaler is unknown since the aerosol dose is much lower than the doses given intravenously.

Although there have been no reports concerning the use of VENTOLIN Inhaler during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information For Patients: The action of VENTOLIN Inhaler may last up to six hours and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking VENTOLIN Inhaler, other inhaled medicines should not be used unless prescribed.

See Illustrated Patient Instructions For Use.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a 2 year study in the rat, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomatas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalational dose. The relevance of these findings to humans is not known. An 18-month study in mice revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects—Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg, corresponding to 1.4, 14, and 140 times the maximum human inhalational dose) showed a cleft palate formation in 5 of 111 (4.5 percent) fetuses at 0.25 mg/kg and in 10 of 108 (9.3 percent) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5 percent) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37 percent) fetuses at 50 mg/kg, corresponding to 2,800 times the maximum human inhalational dose.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS The adverse reactions of albuterol are similar in nature to those of other sympathomimetic agents, although the incidence of certain cardiovascular effects is less with albuterol. A 13-week double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients. The results of this study showed that the incidence of cardiovascular effects was: palpitations, less than 10 per 100 with albuterol and less than 15 per 100 with isoproterenol. The incidences of tachycardia and increased blood pressure were 10 per 100 and less than 5 per 100, respectively, with both drugs. In the same study, both drugs caused tremor or nausea in less than 15 patients per 100, dizziness or heartburn in less than 5 per 100 patients. Nervousness occurred in less than 10 per 100 patients receiving albuterol and in less than 15 per 100 patients receiving isoproterenol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central stimulation, insomnia, headache, unusual taste, and drying or irritation of the oropharynx.

OVERDOSAGE Exaggeration of the effects listed in ADVERSE REACTIONS can occur. Anginal pain and hypertension may result.

The oral LD_{50} in male and female rats and mice was greater than 2,000 mg/kg. The aerosol LD_{50} could not be determined.

Dialysis is not appropriate treatment for overdosage of VENTOLIN Inhaler. The judicious use of a cardioselective beta-receptor blocker, such as metoprolol tartrate, is suggested, bearing in mind the danger of inducing an asthmatic attack.

DOSAGE AND ADMINISTRATION The usual dosage for adults and children 12 years and older is 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended. The use of VENTOLIN Inhaler can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED VENTOLIN Inhaler 17.0 g canister, box of one. Each actuation delivers 90 mcg of albuterol from the mouthpiece. It is supplied with an oral adapter and patient's instructions. (NDC-0173-0321-88)

Store between 15° and 30°C (59° to 86°F).

Glaxo

Manufactured by Glaxo Operations UK, Ltd.,
Greenford, England
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Fort Lauderdale, Florida 33309

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Sarcoidosis: A Clinical, Roentgenographic and Pathological Survey

LT COL VERNON J. NESSAN, MC, USA; JACOB MALIN, MD, *and*
LT COL SAMUEL D. PARKS, MC, USA, *Landstuhl, West Germany*

The records of 107 patients with sarcoidosis were reviewed for clinical presentation, roentgenographic findings and pathological features. Tissue confirmation was obtained in all patients, with transbronchial lung biopsy and minor salivary gland biopsy specimens providing useful procedures for random biopsy when peripheral lymph node or skin lesions were not present. Clinical and laboratory correlations are necessary to exclude other causes of granulomatous disease that may have the same pathological features as sarcoidosis.

SARCOIDOSIS is a multisystem disorder with varied clinical and roentgenographic features. The initial presentation of patients subsequently diagnosed as having sarcoidosis varies from an asymptomatic state to pronounced constitutional symptoms that include fever, weight loss and dyspnea. Tissue confirmation showing noncaseating granulomas in affected organs is frequently sought for histological support for the diagnosis of sarcoidosis. Because other granulomatous disorders can manifest similar clinical and pathological features, cultures and skin testing are required as well.

Of patients with sarcoidosis, 70 percent are younger than 40,[1] with most being 20 to 40 years old at the age of onset.[2] This age group also comprises most of the personnel on active duty in the military. Landstuhl Army Medical Center, Landstuhl, West Germany, serves as a tertiary care referral center for US military forces in southern Europe, Western Europe and the Middle East. A retrospective analysis of all patients referred for suspected sarcoidosis between August 1976 and June 1979 provides an opportunity to review the clinical presentation, roentgenographic findings and pathological features of various biopsy sites selected in the initial evaluation.

Patients and Methods

Patients

From August 1976 to June 1979, a total of 115 patients were referred to the Pulmonary Disease Service for evaluation of suspected sarcoidosis. Eight were found to have other diseases (three usual interstitial pneumonitis, three tuberculosis, one histoplasmosis, one eosinophilic granuloma and one hypersensitivity pneumonitis) and were excluded from this report. In all, 107 were

From the Pulmonary Service (Dr. Nessan) and Department of Pathology (Drs. Malin and Parks), Landstuhl Army Medical Center, Landstuhl, West Germany. Dr. Nessan is now in private practice in Puyallup, Washington; Dr. Malin is is private practice in Reno, Nevada, and Dr. Parks is affiliated with Fitzsimons Army Medical Center, Aurora, Colorado.

The assertions and opinions contained herein are the private views of the authors and do not necessarily reflect the views of the Department of the Army or the Department of Defense.

Submitted, revised, June 1, 1981.

Reprint requests to: Vernon J. Nessan, MD, Puyallup Valley Medical Clinic, 1322-3rd St. SE, Puyallup, WA 98371.

ABBREVIATIONS USED IN TEXT

FVC = forced vital capacity
PPD = purified protein derivative (tuberculin)

subsequently diagnosed as having sarcoidosis on the basis of clinical and roentgenographic presentation, negative cultures and negative skin tests for tuberculosis and fungi. In all patients, confirmation was made from biopsy specimens from at least one organ system.

There were 77 males and 30 females in the study. Of these, 75 men and 10 women were on active duty in the US military. The average age of the patients was 27 with the youngest 10 years old and the oldest 48; 69 patients were black and 38 were white.

Laboratory Investigation

All patients had at least three sputum specimens submitted for tuberculosis and fungus smears and culture. Bronchial washings were also cultured from those patients undergoing fiberoptic bronchoscopy after transbronchial lung biopsy specimens had been obtained. All tissue was routinely processed and sections initially stained with hematoxylin and eosin. From four to eight serial sections were made from biopsy specimens of the transbronchial lung, minor salivary gland and liver. If no granulomas were seen in these initial sections, additional tissue sections were made. Special staining for acid-fast bacilli (Kinyoun carbolfuchsin) and fungi (Gomori's methenamine silver or periodic acid-Schiff) were carried out in each case.

Complete blood counts, liver function tests and calcium, phosphorus and fungal serological tests were carried out in all patients. Serum angiotensin converting enzyme assays were done by Bioscientia (Ingelheim, West Germany). Spirometry and lung volumes by helium dilution were obtained with a Collins modular lung analyzer with a 14-liter spirometer.

Biopsy Procedures

Random biopsy specimens of minor salivary glands were obtained from patients' lower lips in the Oral Surgery Clinic. Peripheral lymph nodes or skin lesions were excised if clinically apparent. If lymph nodes or skin lesions were not apparent, transbronchial lung biopsy specimens were obtained using transnasal fiberoptic bronchoscopy. At least six biopsy specimens were obtained from the lung parenchyma, usually from the anterior segment of the right upper lobe unless other segments appeared more involved on roentgenograms of the chest. Bronchial mucosa was biopsied only if it appeared abnormal on endoscopic examination. Mediastinoscopy was done in those patients who did not have tissue confirmation by any other procedure.

Results

Presenting Symptoms

Of the 107 patients, 37 (34 percent) were asymptomatic at the time of the initial evaluation. Abnormalities were discovered on roentgenograms of the chest obtained either on routine screening examinations or for other unrelated purposes such as trauma (see Table 1). In 39 patients (36 percent) x-ray studies of the chest were made because of respiratory symptoms—chest pain in 5 and persistent cough and dyspnea in 34.

Skin lesions or erythema nodosum led to

TABLE 1.—*Presenting Symptoms by Roentgenographic Stage*

	Stage 0	*Stage I*	*Stage II*	*Stage III*	*Totals*
Asymptomatic	..	23	13	1	37
Respiratory symptoms	..	7	24	8	39
Skin manifestations					
Skin lesions	..	1	..	1	2
Erythema nodosum	..	7	1	..	8
Arthritis/tenosynovitis	..	3	2	..	5
Abdominal symptoms	3	1	..	..	4
Eye symptoms	1	2	..	..	3
Central nervous system symptoms	..	..	1	..	1
Lymphadenopathy	..	1	2	..	3
Uveoparotid fever	..	4	..	..	4
Pericarditis	..	1	..	..	1
TOTAL	4	50	43	10	107

TABLE 2.—*Procedures That Showed Noncaseating Granulomas by Roentgenographic Stage in 107 Patients With Sarcoidosis*

	Stage 0	*Stage I*	*Stage II*	*Stage III*	*Number Positive*	*Number of Procedures Done*
Transbronchial lung biopsy	1	32	35	10	78	85
Mediastinoscopy	..	7	..	..	7	7
Minor salivary gland biopsy	2	22	23	2	49	84
Skin/peripheral lymph node biopsy	..	6	6	1	13	15
Percutaneous liver biopsy	1	..	..	..	1	1
Abdominal lymph node biopsy	1	..	..	..	1	1
Spleen biopsy	1	1	..	..	2	2

evaluation in ten patients. Three of the eight patients with erythema nodosum also had arthralgias or arthritis. Five additional patients had arthralgias or arthritis without erythema nodosum as their initial symptom, involving predominantly the ankle joints. Four patients were referred after abdominal symptoms had resulted in biopsies that showed noncaseating granulomas: one had percutaneous liver biopsy, while three had laparotomies (lymph node involvement in the porta hepatis in one, splenectomies for massively enlarged spleens in the other two). Three of these four had normal findings on roentgenograms of the chest (stage 0).

Three patients with acute iritis were referred from the Ophthalmology Service. During the initial physical examination, eight others were noted to have objective evidence of granulomatous inflammation, although they stated that they did not have any eye symptoms. Of the 11 patients, 4 had anterior uveitis and 7 had posterior uveitis with abnormal findings on fundoscopic examination.

Three patients sought evaluation for peripheral lymphadenopathy; seven additional patients were noted to have peripheral lymphadenopathy on initial physical examination.

Four patients presented with parotid enlargement associated with malaise and elevated temperatures to 38.9°C (102°F) (uveoparotid fever); none of the four had cranial nerve abnormalities associated with the parotid enlargement. One patient (22 years old) presented with central nervous system symptoms of brain stem dysfunction; findings on a roentgenogram of the chest showed stage II sarcoidosis. Biopsy specimens of the lung and minor salivary gland showed noncaseating granulomas; brain biopsy was not done. One patient presented with symptoms and electrocardiographic findings compatible with pericarditis but had no conduction disturbances or congestive heart failure during subsequent evaluation.

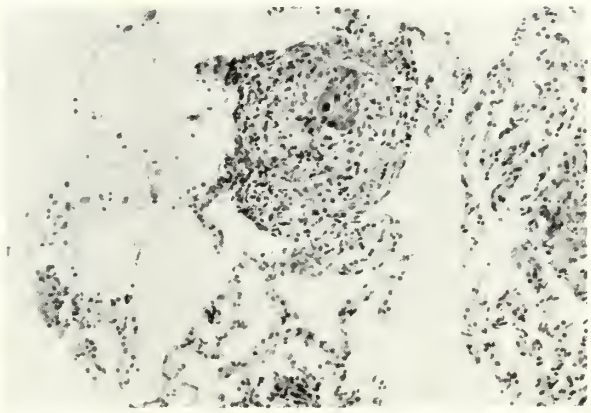

Figure 1.—Transbronchial lung biopsy specimen showing noncaseating granuloma in lung parenchyma. (Hematoxylin-eosin stain; reduced from magnification ×100.)

Biopsy Results

Transbronchial lung biopsies were done in 85 patients; in 78 (92 percent), noncaseating granulomas were noted in lung parenchyma (see Figure 1 and Table 2). In seven patients, normal lung parenchyma or nonspecific interstitial pneumonitis was noted on the fragments (six to eight) of lung tissue obtained. In all seven patients lymph node material obtained at mediastinoscopy was compatible with sarcoidosis.

Minor salivary glands were excised from the inside of the lower lip in 84 patients. In 49, noncaseating granulomas were readily identified (Figure 2). In 44 of the 49 patients biopsy specimens from another site (lung, liver, skin or lymph node) showed granulomatous inflammation. In five, minor salivary gland biopsy specimens provided the only tissue confirmation for sarcoidosis.

Skin or peripheral lymph node biopsies were done in 15 patients. In 2 of 2 skin biopsies and 11 of 13 peripheral lymph node biopsies, findings

were positive—showing well-formed noncaseating epithelioid granulomas. In 12 of the 13 patients with positive findings on lymph node or skin biopsies and in 1 of the 2 patients with negative findings on lymph node or skin biopsies, noncaseating granulomas were detected in minor salivary gland tissue.

Two patients with normal findings on roentgenograms of the chest had hepatic involvement as the main manifestation of sarcoidosis. Abnormal liver function test results were noted for these patients and hepatic biopsies were done. Two other patients had massive splenomegaly with almost total replacement of the spleen by noncaseating granulomas. Three of these four patients also showed minor salivary gland involvement on biopsy specimens.

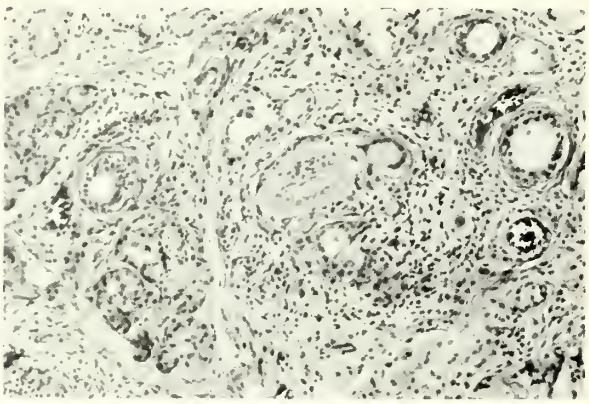

Figure 2.—Noncaseating granuloma in minor salivary gland biopsy specimen, with readily identifiable Langhans' giant cells. (Hematoxylin-eosin stain; reduced from magnification ×100.)

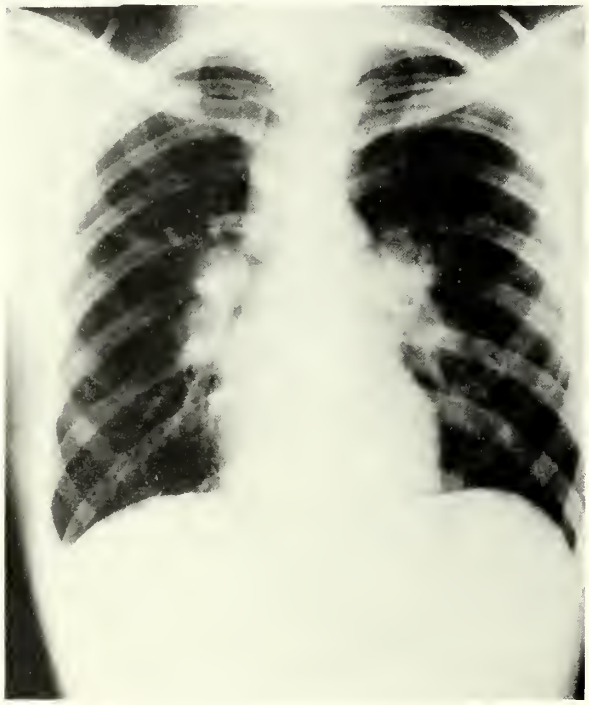

Figure 3.—Roentgenogram showing prominent right paratracheal lymph node enlargement associated with bilateral hilar lymphadenopathy in an asymptomatic male. Spontaneous regression occurred within six months.

Roentgenographic Findings

In four patients no abnormalities were seen on x-ray studies of the chest at initial presentation

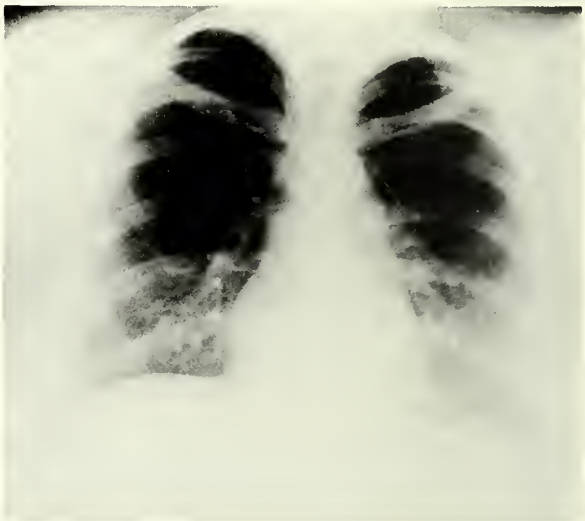

Figure 4.—Roentgenogram showing asymmetrical left hilar and mediastinal lymphadenopathy. Skin tests and cultures were negative; however, transbronchial lung and minor salivary gland biopsy specimens showed noncaseating granuloma compatible with sarcoidosis.

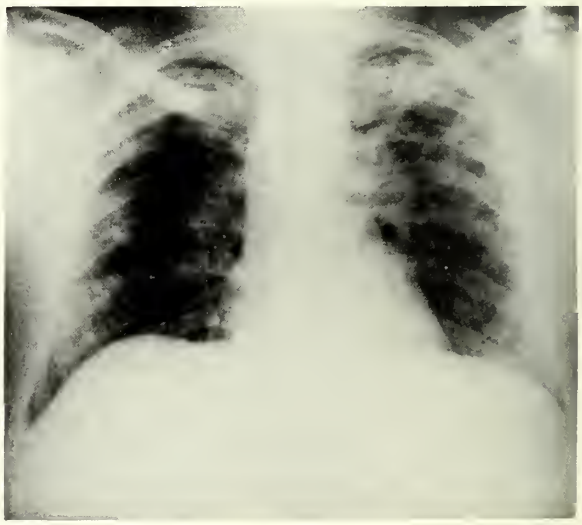

Figure 5.—Roentgenogram showing bilateral hilar lymphadenopathy with diffuse interstitial infiltrates (stage II).

(stage 0). Three had abdominal sarcoidosis involving spleen or liver, while the fourth patient presented with posterior uveitis. Multisystem involvement was documented by random minor salivary gland biopsy in three of these patients and by transbronchial lung biopsy in one.

Fifty patients had evidence of hilar and mediastinal lymphadenopathy without parenchymal infiltrates (stage I) on roentgenograms of the chest. In 44 patients findings showed "typical" bilateral hilar lymphadenopathy with or without right paratracheal node enlargement (Figure 3). Four patients had asymmetrical hilar lymphadenopathy (Figure 4); two patients had mediastinal lymphadenopathy without hilar enlargement, and one patient had a transient right-sided pleural effusion associated with bilateral hilar adenopathy.

Forty-two patients had parenchymal infiltrates in addition to hilar or mediastinal lymph node enlargement (stage II), predominantly in the upper lobes. Five patients had right upper lobe infiltrates alone. Three had left upper lobe infiltrates and 34 had diffuse bilateral disease (Figure 5). Parenchymal changes noted were an increase in interstitial markings in 31, reticlonodular pattern in 5 and a predominantly alveolar pattern in 6 patients.

Figure 6.—Roentgenogram showing stage III sarcoidosis with diffuse alveolar infiltrates with no demonstrable hilar enlargement apparent on posterior-anterior or lateral view (not shown).

Eleven patients with parenchymal infiltrates without hilar or mediastinal lymphadenopathy (stage III) all had diffuse upper and lower lobe involvement. Seven patients had increased interstitial markings, while four had alveolar infiltrates (Figure 6).

Laboratory Findings

The leukocyte count averaged 6,400 per cu mm, ranging from 3,200 to 10,400 per cu mm. Alkaline phosphatase or serum aspartate aminotransferase levels were elevated in nine patients (five with stage II and four with stage III disease). Serum calcium levels were persistently elevated to 11.2 mg per dl in only one patient with normal 24-hour urinary calcium and parathyroid hormone levels.

Pulmonary function test results fell within normal limits in 89 patients but were abnormal in 18. In nine forced vital capacity (FVC) was less than 80 percent of predicted; nine others had FVC less than 60 percent of predicted. The nine patients with less than 70 percent of predicted FVC also had alveolar-arterial oxygen differences of greater than 30 mm of mercury. The predominant pattern was one of restriction, with 13 of the 18 patients exhibiting normal flow rates; 5 of the 18 patients had an associated obstructive pattern with a forced expiratory volume in one second (FEV_1) and maximal midexpiratory flow of less than 70 percent of predicted values.

Serum angiotensin-converting enzyme levels were elevated in 25 of 32 patients. Of the seven with normal values, five were asymptomatic at the time of evaluation and were referred on the basis of the roentgenograms of the chest alone.

Pathological Findings

The primary histological criterion for the diagnosis to be consistent with sarcoidosis was discrete noncaseating granulomas. These contained epithelioid cells, Langhans' giant cells and lymphocytes. Occasional granulomas in the spleens and lymph nodes also showed mild fiibrinoid necrosis. In all cases, no fungi or acid-fast bacilli were detected by special stains. Nonspecific giant cell inclusions were occasionally seen in all tissues except the minor salivary glands. These included

Schaumann's bodies, asteroid bodies and polarizable crystals (probably calcium oxalate).

Bronchoscopic Findings

Endobronchial examination results were either normal or showed mild to moderate edema or erythema, or both, in 92 patients. In six patients with stage I disease and nine patients with stage II disease, endobronchial granularity with 1- to 2-mm yellowish-white nodules surrounded by erythema were noted. When biopsied, these bronchial nodules showed submucosal noncaseating granulomas.

Corticosteroid Administration

Prednisone was administered to 24 patients within two months of diagnosis. Ten patients with stage II and five with stage III disease received steroid therapy, based on respiratory symptoms and pulmonary function abnormalities. In four patients posterior uveitis was treated with systemic corticosteroids (four with anterior uveitis received topical steroids alone). Corticosteroids were also administered to three of the patients with abdominal sarcoidosis and two patients with severe ankle tenosynovitis that was unresponsive to nonsteroidal anti-inflammatory agents.

Discussion

The predominance of males (greater than 2:1) in this series reflects the military population served by Landstuhl Army Medical Center. This population is highly mobile, making long-term follow-up difficult and tissue diagnosis at the time of initial evaluation more desirable.

The selection of a biopsy site for tissue confirmation is in part dependent on what is discovered at physical examination at the time of presentation. In 13 of 15 patients (86 percent) in whom peripheral lymph nodes or skin lesions were apparent, there were positive biopsy results. However, this represented only 14 percent of the total number of patients in this series.

Random biopsies of minor salivary glands from the lower lip provide a readily accessible site for histological confirmation with low risk and minimum morbidity.[3] An overall yield of positive biopsy results of 58 percent (49 of 84 patients) in this series has made the minor salivary gland our choice as the initial biopsy site in all patients who present with suspected sarcoidosis. If noncaseating granulomas are found on biopsy and no other cause has been defined in a patient with a compatible clinical and roentgenographic presentation, more invasive procedures may not be necessary. It also serves as a readily accessible site to check multi-system involvement if a biopsy specimen from another organ (lung, liver, skin or lymph node) also shows noncaseating granulomas.

Transbronchial lung biopsies, using the fiberoptic bronchoscope, are often done to support the diagnosis of sarcoidosis because of the high yield of noncaseating granulomas in lung parenchyma. The procedure also provides additional culture material available from bronchial washings. When at least four random lung biopsy specimens are obtained, noncaseating granulomas have been reported in 77 percent of patients with sarcoidosis.[4-7] In this series 78 of 85 patients (92 percent) in whom transbronchial lung biopsies were done had positive findings in at least one of the biopsy specimens. This higher yield is explained by more biopsy specimens[3,8,9] obtained from each patient and correlates well with other recent studies.[10,11] In stage II and III disease, where parenchymal involvement is ascertained by findings on roentgenograms of the chest, 45 of 45 cases (100 percent) showed noncaseating granulomas on pathological examination. Numerous tissue sections of the biopsy material may be necessary. This is especially important with the transbronchial lung and minor salivary gland biopsies were the amount of biopsy tissue is small; as many as 15 sections were sometimes necessary before granulomas were identified.

If histological confirmation has not been obtained after the above procedures, mediastinoscopy is done to obtain tissue specimens for histological examination and culture. All seven patients in this series who had mediastinoscopy had positive biopsy results.

The x-ray pattern in sarcoidosis is widely varied, with prognosis based to some extent on roentgenographic stage. Approximately 60 percent of patients with roentgenographic stage I, 46 percent with stage II, and 26 percent with stage III will have eventual resolution of the condition.[1] Roentgenographic staging is used primarily for comparison purposes and does not imply that the disease advances from stage I to stage II or III; symptoms and disability are also not necessarily related to roentgenographic stage. In this series, the patients with most severe constitutional

symptoms (fatigue, loss of weight and night sweats) all had stage I disease.

On the other hand, all 15 patients in this series who were treated with corticosteroids to control respiratory symptoms had stage II or stage III roentgenographic changes and moderate to severe reduction in pulmonary function.

Measuring serum angiotensin-converting enzyme levels has been used to assess the activity of sarcoidosis; levels are usually elevated in patients with active disease and normal in those with inactive sarcoidosis or in those receiving steroids.[8,12,13] In the seven patients in this series with normal levels of serum angiotensin-converting enzyme, only two presented with active clinical processes (erythema nodosum and anterior uveitis). The remaining five were referred on the basis of abnormal findings on screening x-ray studies of the chest. This may imply that their disease was entering an inactive phase at the time of initial evaluation, even though biopsy specimens showed well-formed noncaseating granulomas.

Two patients with stage I roentgenographic changes had evidence of previous tuberculous infection manifested by a positive intermediate purified protein derivative (PPD) tuberculin skin test and normal findings on roentgenograms of the chest before referral. Skin test reactivity was maintained at the time of evaluation; multiple sputum specimens and bronchial washings were negative in both patients. One patient had a tuberculin-positive test at the time of referral, with a negative tuberculin skin test 18 months earlier. Two patients (not included in this series) had *Mycobacterium tuberculosis* on cultures grown from bronchial washings in one and a peripheral lymph node in one. Intermediate PPD tests were negative in both patients.

Conclusions

The results of our study emphasize that the diagnosis of sarcoidosis requires clinical and pathological correlation. Noncaseating granulomas may be found in patients with tuberculosis if only a small amount of biopsy material is examined. The distinction between caseating and noncaseating granulomas may be difficult to make. For example, biopsy specimens showing granulomas that contain fibrinoid or granular necrosis may be interpreted as caseous necrosis.[7] Fibrinoid necrosis, frequently found in the center of coalescence of granulomas, is eosinophilic, fibrillar or granular, and acellular, with a few scattered lymphocytes at the periphery. Similar descriptions are compatible with caseous necrosis.

Other causes of granulomatous infection found during investigation for sarcoidosis require treatment, while specific therapy for sarcoidosis has not been defined and corticosteroid therapy is controversial.[14] Sarcoidosis remains a diagnosis best supported by clinical, roentgenographic and pathological correlation after other causes have been excluded.

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Refer to: Landers D: Unsuccessful suicide by carbon monoxide: A secondary benefit of emissions control. West J Med 135:360-363, Nov 1981

Unsuccessful Suicide by Carbon Monoxide: A Secondary Benefit of Emissions Control

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Emission systems and devices are required on automobile engines to reduce air pollution problems. Catalytic converters have been used on most 1975 and newer automobiles to reduce hydrocarbon and carbon monoxide (CO) emissions to a value that meets the Environmental Protection Agency requirements established for 1975 and 1976. The 1980-1981 Boise, Idaho, study shows that with a functioning catalytic converter either unmeasurable or sublethal quantities of CO appear in automobile exhaust. Thus, emissions control has produced a secondary benefit in reducing the number of suicides by CO poisoning from automobile exhaust fumes.

CARBON MONOXIDE (CO) POISONING has been responsible for many accidental deaths as well as serving as an extremely effective, relatively nondisfiguring, and easily accessible method of suicide. It is responsible for half of the fatal poisonings in the United States.[1] Because of the toxicity of the domestic gas supply in Great Britain, suicidal persons there traditionally have "put their heads in the gas oven" to commit suicide.[2] In the United States the traditional means of intentional carbon monoxide poisoning has been inhalation of car-exhaust fumes.[1,3] It has previously been shown that automobile exhaust will saturate the car's interior or the interior of a small garage in 15 minutes to half an hour with a lethal amount of carbon monoxide.[1] The addition of emission systems on automobile engines, however, has resulted in substantially reducing the amount of CO in auto exhaust and, in turn, has reduced the number of deaths from inhalation of these fumes. We present one such case.

Report of a Case

A 35-year-old man was brought to the Emergency Department by paramedics after having been found lying unconscious in a closed garage behind a running 1980 four-cylinder Chevrolet Chevette. The patient had been lying 12 inches from the exhaust pipe, with the car running, for at least three hours before being pulled from the garage. The patient initially had minimal respiratory effort; however, after being pulled from the garage into the cool morning air, his respirations slowly increased. When the paramedics arrived, they found him awake, with vital signs as follows: blood pressure 132/72 mm of mercury, pulse 100 beats per minute and respiratory rate 24 breaths per minute. The skin of his face and his oral mucous membranes were red. He was retching, but no vomitus was noted. The air inside the

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ABBREVIATIONS USED IN TEXT

CO = carbon monoxide
HC = hydrocarbons

garage was thick with exhaust fumes, which had caused considerable irritation to the man's eyes and respiratory tract.

When the patient was examined in the Emergency Department, blood pressure was 142/92 mm of mercury, pulse 100 beats per minute and respirations 28 per minute. There was some residual redness of the face, and he was awake but voluntarily not speaking. He was given 100 percent oxygen by face mask, and his lungs were clear to auscultation and percussion.

Laboratory evaluation showed hemoglobin to be 16.8 grams per dl and the leukocyte count 8,100 per cu mm. An SMAC screen gave all normal values. Arterial blood gas determinations gave the following values: pH 7.34, bicarbonate 23 mEq per liter, partial pressure of carbon dioxide 42 and partial pressure of oxygen 116 mm of mercury, and oxygen saturation 72 percent. The carboxyhemoglobin was 36 percent and the level of alcohol in the blood was recorded at 0.09 grams per dl.

After initial evaluation and treatment in the Emergency Department, the patient was transferred to the mental health unit where he remained in hospital for ten days before being dismissed without neurological sequelae.

Discussion

Emission control systems and devices have been installed on automobile engines to reduce products of combustion—specifically, carbon monoxide (CO), hydrocarbons (HC) and oxides of nitrogen. Since 1975 automobile manufacturers have used catalytic converters (Figure 1) to reduce HC and CO emissions to a value that meets the Environmental Protection Agency standards.[4]

The catalytic converter works by providing an additional area to oxidize or burn the HC and CO after it leaves the engine. It is a component that looks much like a muffler and is located between the engine block and the muffler. This system uses platinum and palladium as a catalyst to speed up the change of HC and CO to water and carbon dioxide (Figure 2).

While automobile manufacturers' recommended standards since 1975 have allowed up to 1 percent CO exhaust emission for catalytic-equipped automobiles (Table 1), most of the vehicles studied in the 1980-1981 Idaho Auto Emissions test gave values of less than 0.5 percent CO.[5] As shown in Table 2, many 1980 Chevrolets that were studied, using a SUN EPA Model 75 electronic gas analyzer, did not put out enough carbon monoxide to register on the machine. The analyzer used was a solid-state, nondispersive infrared exhaust analyzer that measures levels of HC and CO in the exhaust of an internal combustion engine. CO levels can be measured between 0 and 10 percent with a cross-sensitivity level of less than 0.1 percent of full scale reading on the CO meter measured against a 15 percent carbon dioxide sample. The complete system is accurate overall to ±2.5 percent of full scale reading and is the standard detector used to measure HC and CO concentrations in exhaust fumes.

The findings from all 33 of the 1980 Chevrolets tested in the 1980-1981 Idaho Auto Emissions

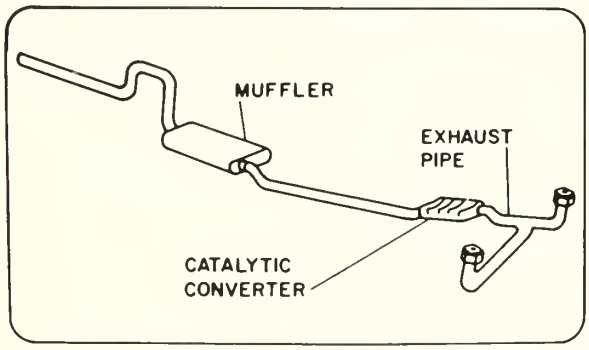

Figure 1.—Single exhaust system with catalytic converter. (From EPA-450, Motor Vehicle Emissions Control Book 7.)

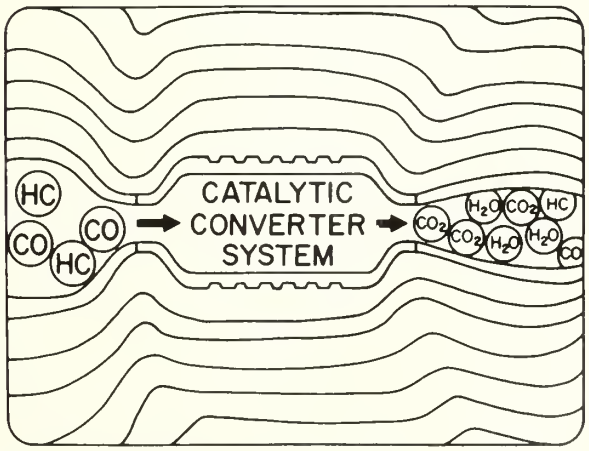

Figure 2.—Catalytic converter system, showing conversion of carbon monoxide (CO) and hydrocarbons (HC) to carbon dioxide (CO_2) and water (H_2O). (From EPA-450, Motor Vehicle Emissions Control Book 7.)

Study are as follows: unmeasurable amounts of CO in 12 of the vehicles; 0-0.1 percent CO in 14 of the vehicles, and greater than 0.1 percent CO in 7 of the vehicles.

The toxic effect of carbon monoxide on animals has probably been known by man since the discovery of fire. However, it remained for Haldane to show that the main toxic property of carbon monoxide is its ability to bind to hemoglobin to a much higher degree than oxygen. Although oxygen combines with hemoglobin ten times more readily than CO, oxygen also dissociates from hemoglobin 2,400 times more rapidly than carbon monoxide. Thus, the affinity of carbon monoxide for hemoglobin is 240 times greater than it is for oxygen.[6-8]

Because carbon monoxide competes with oxygen for binding sites on the hemoglobin, the oxyhemoglobin saturation is decreased. It is important to realize the oxygen tension (Po_2) will remain near normal, but oxygen content (or saturation) will fall sharply as oxygen is replaced by carbon monoxide in the hemoglobin molecule.[6,7] In addition to the reduced oxyhemoglobin saturation, the oxyhemoglobin dissociation curve is shifted to the left so that oxygen cannot be released from the hemoglobin unless a dangerously low oxygen tension exists in the tissues (Figure 3).[8,9]

Carbon monoxide has been shown to have little

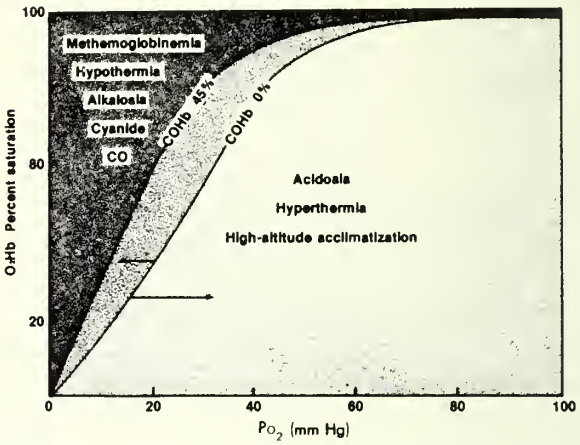

Figure 3.—Oxygen-hemoglobin dissociation curve (CO = carbon monoxide; COHb = carboxyhemoglobin; O_2Hb = oxyhemoglobin; Po_2 = partial pressure of oxygen). (Reproduced with permission from *Hospital Practice* 2: 48-72, Feb 1981, by Peter Frishauf, Editor.)

TABLE 1.—*Automobile Manufacturers' Exhaust Emissions Standards*

Voluntary inspection standards

Model Year of Vehicle	*CO (percent)*
Pre-1968	8.5
1968-1969	7.0
1970-1974	5.0
1975-1979	3.0

Manufacturers' recommended standards (vehicle tuned to manufacturers' specifications)

Model Year of Vehicle	*CO (percent)*	*HC (ppm)*
1975-1979 Noncatalytic	1.5	150
1975-1979 Catalytic equipped	1.0	75

CO = carbon monoxide; HC = hydrocarbons

TABLE 2.—*Findings of the 1980-1981 Idaho Emissions Study for 1980 Chevrolets**

1980 Chevrolet	*CO (percent)*	*HC (ppm)*
1	0.00	50
2	0.10	10
3	0.00	0
4	0.10	25
5	0.00	50
6	0.00	0
7	0.10	200
8	0.10	10
9	0.00	50
10	0.00	25

CO = carbon monoxide; HC = hydrocarbons

*Partial list of 1980 Chevrolets tested in Boise, Idaho, study.

TABLE 3.—*Correlation Between CO Concentration and the Signs and Symptoms of CO Poisoning**

Percent CO in Atmosphere	*COHb Concentration (percent)*	*Signs and Symptoms*
	0-10	None (angina may be noted in patients with coronary artery disease).
0.007	10-20	Slight headache, exercise-induced angina, dyspnea on vigorous exertion.
0.012	20-30	Throbbing headache, dyspnea on moderate exertion.
0.022	30-40	Severe headache, nausea, vomiting, weakness, visual disturbance, impaired judgment.
0.035-0.052	40-50	Syncope, tachycardia, tachypnea.
	50-60	Coma, convulsions, Cheyne-Stokes respiration.
0.080-0.122	60-70	Compromised cardiorespiratory function.
0.195	70-80	Death.

NOTE: If the rise in COHb level has been unusually rapid, coma may ensue before other symptoms become apparent. Symptoms correlate best with the maximal pretreatment levels.

CO = carbon monoxide; COHb = carboxyhemoglobin.

*Modified after Haldane and reproduced with permission from *Hospital Practice* 2:48-72, Feb 1981, by Peter Frishauf, Editor.

in the way of a true toxic effect. Rather, the tissue damage from CO is a result of hypoxia. Factors that may contribute to toxicity include total carboxyhemoglobin concentrations, length of exposure, metabolic activity during exposure, underlying disease states and presence of alcohol.[9,10]

The correlation between CO concentration and symptoms of CO poisoning is shown in Table 3. The symptoms of carbon monoxide poisoning are subtle and may range from slight headache and exercise-induced angina to severe headache with nausea and vomiting. On physical examination, cherry pink or red discoloration of the skin and mucous membranes, tachycardia and tachypnea may be noted. These symptoms progress to unconsciousness at a level of 40 percent to 50 percent carboxyhemoglobin concentration, which may be reached with as little as 0.035 percent to 0.052 percent CO in the atmosphere.[9]

Treatment for carbon monoxide poisoning consists of the administration of high-flow oxygen to hasten carboxyhemoglobin dissociation.[12] It has been shown that the excretion of carbon monoxide, like its absorption, is entirely through the respiratory system and that the elimination of CO follows an exponential time curve.[9-11] When ambient air is breathed, the carboxyhemoglobin concentration falls by half in approximately 250 minutes. When high-flow oxygen is administered, the concentration of carboxyhemoglobin is reduced by half during each 40-minute treatment period.[9,11] Using this rule of thumb, it can be assumed that our patient had a maximum carboxyhemoglobin level of between 55 percent and 65 percent, with about 0.080 percent CO in the atmosphere. These figures are compatible with those obtained from the emission tests for 1980 Chevrolets in the Idaho study.

Conclusion

Reduction in suicides can be shown to be the result of primary prevention—that is, improved knowledge and treatment of psychiatric illness—and secondary prevention—reduction in the lethality of traditional methods of suicide.[2] In this case, secondary prevention of suicide is aptly demonstrated, and represents a significant and heretofore unrecognized benefit of emissions control.

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Risk of Altitude Exposure in Sickle Cell Disease

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The risk of altitude-induced hypoxemia causing painful crisis was determined in a group of 45 predominantly adult patients with sickle cell disease. The patients were divided into two groups: those with hemoglobin (Hb) SS and those with Hb SC or Hb S β-thalassemia. Altitude exposures were divided into airplane travel and mountain visits, and the latter subdivided into stays at 4,400 or 6,320 ft. The average risk of crisis was higher for both groups while in the mountains (37.9 percent and 56.6 percent, respectively) than it was during airplane travel (10.8 percent and 13.5 percent, respectively). The latter group had more splenic crises than the former group and also had a greater risk at 6,320 ft (65.9 percent) than at 4,400 ft (20.0 percent). Patients with sickle cell disease are at high risk of crisis in the mountains, and we advise those with intact spleens to breathe supplemental oxygen during air travel.

It is well established that manifestations of sickle cell disease are exacerbated by hypoxemia.[1] Several case reports indicate that not only these patients but those with only sickle trait are thought to be at increased risk during airplane travel[2,3] and while in the mountains.[4-6]

A group of pediatric and adult patients with sickle cell disease was reported to have a 20 percent to 30 percent incidence of a crisis with exposure to travel in the mountains or in pressurized aircraft.[7] Those in that study, however, were already acclimatized to altitude by virtue of residing at an elevation of 5,000 ft above sea level; thus, their experience may not accurately reflect the risk of most patients with sickle cell disease. We studied a largely adult population of patients with sickle cell disease who reside near sea level in San Francisco; the results are reported herein.

Patients and Methods

We studied retrospectively 45 patients with sickle cell disease who had a history of high altitude exposure. Of these, 38 were followed up at the San Francisco General Hospital Hematology Clinic and 7 were followed up at other centers in San Francisco. Twenty-six patients were homozygous for hemoglobin (Hb) S, 13 were doubly heterozygous for Hb S and Hb C, and 6 were doubly heterozygous for Hb S and β-thalassemia. Hb A, Hb S and Hb C concentrations were deter-

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TABLE 1.—*The Risk of Splenic, Nonsplenic and Total Painful Crises During Mountain and Air Travel in Patients With Sickle Cell Disease*

Group	Painful Events/Patient			Painful Events/Times at Risk			Average Risk	
	Splenic Crisis	Nonsplenic Crisis	Total	Splenic Crisis	Nonsplenic Crisis	Total	Nonsplenic Crisis (percent)	Total (percent)
Mountain exposure								
Hb SS	0/12 (0.0%)	6/12 (50.0%)	6/12 (50.0%)	0/35 (0.0%)	6/35 (17.1%)	6/35 (17.1%)	37.9	37.9
Hb SC/Hb S β-thal	4/14 (28.6%)	5/14 (35.7%)	9/14 (64.3%)	4/59 (6.8%)	18/59 (30.5%)	22/59 (37.3%)	28.1	56.6
Air travel								
Hb SS	1/23 (4.3%)	2/23 (8.7%)	3/23 (13.0%)	1/221 (0.5%)	2/221 (0.9%)	3/221 (1.4%)	6.5	10.8
Hb SC/Hb S β-thal	4/17 (23.5%)	2/17 (11.8%)	6/17 (35.3%)	4/443 (0.9%)	23/443 (5.2%)	27/443 (6.1%)	5.5	13.5

β-thal = β-thalassemia

mined by hemoglobin electrophoresis; concentration of Hb A_2 was determined by column chromatography,[8,9] Hb F concentration was determined by alkaline denaturation.[10] Erythrocyte indices were determined by the Coulter Model S. The patients ranged in age from 10 to 62 years, with only five under the age of 18—two with Hb SC and three with Hb SS. The youngest patient with Hb SS was ten years old. All patients lived near sea level in San Francisco.

Because of the vulnerability of the spleen to infarctive crisis, the patients were divided into two groups: those with Hb SS, who generally, as adults, have splenic atrophy,[11] and those with Hb SC or Hb S β-thalassemia, who generally have normal-sized or enlarged spleens. Altitude exposures were divided into airplane travel and visits to the mountains, during which no strenuous physical exertion such as mountain climbing was undertaken. With the exception of one flight by a patient with Hb SS in an unpressurized aircraft, all flights were in commercial pressurized planes. Air travel time varied from 1 to 6 hours, except for one international flight of 14 hours.

One of us (M.G.) asked each patient to recall the total number of mountain or airplane experiences and the number that resulted in painful episodes. An altitude-related painful crisis was defined as moderate to severe pain in the extremities, back, chest or abdomen that occurred during or immediately after exposure to high altitude. We did not require hospital admittance or physician verification of a painful episode but relied on the patients' recollections. Left upper quadrant abdominal pain as the primary symptom complex was considered to be a probable splenic crisis. Nonspecific symptoms such as dizziness and headache were not considered to be altitude-related events. To assess the risk of hypoxemia in a more quantitative manner, we compared the risk of crisis in patients whose mountain visits were to Reno, Nevada, (elevation 4,400 ft) with those whose visits were to Lake Tahoe, Nevada, (elevation 6,320 ft). None of the crises reported to occur in the mountains occurred while patients were in transit over higher mountain passages to these areas—all occurred while patients were in Reno or at Lake Tahoe.

We assessed the information in three ways. First, we determined the fraction of patients who had a positive history of crisis with altitude exposure. Second, we determined the fraction of total times at risk that resulted in a crisis. Finally, because both of the above determinations may be skewed by patients with unusually severe or unusually mild clinical courses, we calculated the average risk per patient by determining for each patient the number of crises per times at risk, determining the sum of these fractions from all of the patients in each group, and dividing this sum by the number of patients in each group:

$$\text{Average risk} = \frac{\Sigma\left(\frac{\text{crises}_1}{\text{exposures}_1}\right) + \left(\frac{\text{crises}_2}{\text{exposures}_2}\right) \ldots + \left(\frac{\text{crises}_n}{\text{exposures}_n}\right)}{n}$$

Results

Results of analyses of painful crises occurring during mountain travel are shown in Table 1. In 50 percent of the patients with Hb SS and in 64.3 percent of the patients with Hb SC disease or Hb S β-thalassemia, painful crises occurred during travel in the mountains. When the occurrence of painful crises during mountain travel was

assessed in terms of the total number of times at risk, both groups had a lower frequency of crises, a finding that reflects that patients who had had a crisis during initial mountain travel tended to avoid further exposure. Of the exposures, 17.1 percent resulted in painful crises for the Hb SS group and 37.3 percent for the Hb SC disease and Hb S β-thalassemia group. The average risk of crisis per patient was 37.9 percent for Hb SS and 56.6 percent for patients with Hb SC disease or Hb β-thalassemia.

The analysis of painful crises occurring during airplane travel are also shown in Table 1. In 13 percent of the patients with Hb SS and in 35.3 percent of the patients with Hb SC or Hb S β-thalassemia, painful crises occurred during airplane travel. The percent of the exposures that resulted in painful crises were 1.4 percent in the former group and 6.1 percent in the latter group. Again, these lower frequencies reflect a tendency to avoid further exposure after an initial painful crisis. The average risk of crisis per patient was 10.8 percent for the Hb SS group and 13.5 percent for the Hb SC and Hb S β-thalassemia group.

No splenic crisis occurred during mountain exposure in those with Hb SS, but crisis occurred in 28.6 percent of those with Hb SC or Hb S β-thalassemia and in 6.8 percent of their exposures. During air travel 4.3 percent of patients with Hb SS (0.5 percent of their flights) had a splenic crisis. Splenic crisis occurred in 23.5 percent of patients with Hb SC or Hb S β-thalassemia (0.9 percent of their flights).

Subtracting the number of splenic crises from the total number of painful episodes showed that the risk of nonsplenic crisis is similar in both groups for both types of hypoxic exposures (Table 1). During air travel nonsplenic crises ocurred in 8.7 percent of the Hb SS patients and in 0.9 percent of their flights; their average risk of nonsplenic crisis was 6.5 percent. Air travel resulted in nonsplenic crises in 11.8 percent of the Hb SC or Hb S β-thalassemia patients and in 5.2 percent of their flights; their average risk of nonsplenic crisis was 5.5 percent. During mountain exposure nonsplenic crises occurred in 50 percent of those with Hb SS and in 17.1 percent of their visits, and their average risk of nonsplenic crisis was 37.9 percent. Mountain exposure resulted in nonsplenic crises in 35.7 percent of those with Hb SC or Hb S β-thalassemia and in 30.5 percent of their mountain visits, and their average risk of nonsplenic crisis was 28.1 percent.

TABLE 2.—*The Risk of Painful Crisis in Patients With Sickle Cell Disease During Mountain Exposure at Lake Tahoe (6,320 ft) and in Reno (4,400 ft)*

Exposure Site	*Events/ Patient*	*Events/ Times at Risk*	*Average Risk (percent)*
Exposure of SS group to different altitudes			
Lake Tahoe ..	3/5 (60.0%)	3/25 (12.0%)	31.0
Reno	3/7 (42.9%)	3/10 (30.0%)	42.9
Exposure of the SC/S β-thalassemia group to different altitudes			
Lake Tahoe ..	7/9 (77.8%)	20/32 (62.5%)	65.9
Reno	2/5 (40.0%)	2/27 (7.4%)	20.0

Results of a comparison between events at Lake Tahoe and in Reno are shown in Table 2. Of the patients with Hb SS, 60 percent had a crisis while at 6,320 ft and 42.9 percent had a crisis at 4,400 ft. The percentage of events per times at risk was 12 percent at Lake Tahoe and 30 percent in Reno. Their average risk of having a crisis was 31 percent at 6,320 ft and 42.9 percent at 4,400 ft. Of the patients with Hb SC or Hb S β-thalassemia, 77.8 had a crisis at 6,320 ft and 40 percent had a crisis at 4,400 ft. The percentage of events per times at risk was 62.5 percent at Lake Tahoe and 7.4 percent in Reno. Their average risk of having a crisis was 65.9 percent at 6,320 ft and 20 percent at 4,400 ft.

Discussion

In our study, mountain travel presented substantial risk of a painful crisis to both groups of patients. And, while airplane travel resulted in few painful crises in patients with Hb SS, those with Hb SC or Hb S β-thalassemia (especially those with splenomegaly) had substantial risk of a painful crisis (although less than during mountain travel).

Ascent to mountain elevations or travel in commercial pressurized planes that maintain cabin pressure at 5,000 to 7,000 feet[2] is associated with a drop in oxygen pressure (Po_2) that may adversely affect patients with Hb S. Another risk of altitude is its effect on Hb-oxygen affinity. In nonsickle subjects the initial increase in affinity caused by respiratory alkalosis[1] is followed in 12 hours by an overall decrease in affinity due to elevations of 2,3-diphosphoglycerate levels.[12,13] If such a course occurs in sickle patients, who have baseline elevations in 2,3-diphosphoglycerate levels,[14,15] it could explain the higher incidence of

crisis during the longer exposure of mountain visits, as compared with airplane flights. This may also be the explanation for why the only flight that lasted longer than 12 hours resulted in a crisis in the patient.

Our comparison of mountain travel locations indicated no consistent difference between risks at Lake Tahoe and in Reno for Hb SS patients. However, there was a much higher incidence of painful events at 6,320 ft than at 4,400 ft for patients with Hb SC or Hb S β-thalassemia.

Only patients with an intact spleen had symptoms consistent with splenic crisis at high altitude. Although it has been suggested that splenic crisis during airplane travel may be related to inactivity and the wearing of seatbelts,[2,3] in our survey splenic crisis ocurred more frequently during mountain exposure (4/94 or 4.3 percent) than during airplane flight (5/664 or 0.75 percent). Most of the patients in whom splenic crisis developed had Hb SC or Hb S β-thalassemia, and all had enlarged spleens. There were, however, three patients in our study with splenomegaly who did not have any splenic pain during either airplane or mountain exposure. The only splenic crisis occurring among patients with Hb SS occurred after a 14-hour airplane flight in a Saudi Arabian patient with splenomegaly and an Hb F level of 26 percent. The fact that splenic infarction during air travel appears to be a previously unreported event in adults with Hb SS is attributable to the presence of autoinfarcted spleens in most such patients.[15]

The experiences of our patients during altitude exposure were remarkably variable. All those who had a splenic crisis did so only once, and none repeated that exposure. One patient with Hb SC had a splenectomy after a splenic crisis while in flight and has since flown without problems. Another patient with Hb SC had a splenic crisis during his only trip to the mountains after 150 airplane flights without incident. One patient with Hb SS had flown 70 times but had a painful crisis only in the mountains. A small number of patients made repeated trips to the mountains or took flights despite a painful crisis with virtually every exposure, but most patients who had problems at high altitude subsequently avoided such exposure. This tendency to avoid the cause of previous crises was responsible for the difference between the crisis per total exposure ratio and the crisis per patient ratio. Both of these estimates of risk can be skewed by patients whose individual risk at high altitude is unusually severe or unusually mild. To avoid this bias, we calculated the average risk per patient: the average risk was higher in the Hb SC or Hb S β-thalassemia group and seemed to reflect the greater incidence of intact spleens and associated splenic crises in this group. This was corroborated by a similar incidence of crisis for this and the Hb SS group when the number of splenic events was subtracted from both.

Patients from Denver with sickle cell disease have been shown to have a similar risk of crisis during both air travel and mountain exposure.[7] Our study not only confirms this risk, but also, paradoxically, shows an even higher incidence of risk for patients who live at sea level and who, presumably, have lower levels of 2,3-diphosphoglycerate. The reason why living at high altitude should create a protective effect is not clear.

Conclusion

To diminish the risk of crisis, patients with sickle cell disease should be advised to remain well hydrated during hypoxic exposure. Based on our data, all patients with sickle cell disease who have had no previous mountain exposure should be advised to avoid the mountains, and patients with Hb SC or Hb S β-thalassemia who have splenomegaly should arrange in advance for in-flight oxygen. We believe that adult patients with Hb SS do not need supplemental oxygen unless they are among the 6 percent[11] of adult patients with Hb SS and intact spleens.

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Pancreatic Exocrine Function Testing

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It is important to understand which pancreatic function tests are available and how to interpret them when evaluating patients with malabsorption. Available direct tests are the secretin stimulation test, the Lundh test meal, and measurement of serum or fecal enzymes. Indirect tests assess pancreatic exocrine function by measuring the effect of pancreatic secretion on various nutrients. These include triglycerides labeled with carbon 14, cobalamin labeled with cobalt 57 and cobalt 58, and para-aminobenzoic acid bound to a dipeptide. Of all these tests the secretin stimulation test is the most accurate and reliable if done by experienced personnel. However, the indirect tests are simpler to do and appear to be comparable to the secretin test at detecting pancreatic exocrine insufficiency. These indirect tests are becoming clinically available and clinicians should familiarize themselves with the strengths and weaknesses of each.

EXOCRINE FUNCTION of the pancreas is required for digestion of fat, protein and carbohydrates. For efficient digestion the pancreas must secrete bicarbonate as well as enzymes. Because the major enzymes secreted by the pancreas (amylase, trypsin, chymotrypsin and lipase) are denatured by acid or the combination of acid and pepsin, maldigestion can occur if bicarbonate secretion is diminished, even though the enzymes are present in adequate concentrations. Impaired secretion of pancreatic enzymes, bicarbonate, or both, results either from diffuse destruction of the gland (usually the result of chronic relapsing pancreatitis) or from obstruction of the main duct in the head of the pancreas by carcinoma or stricture.

It is often difficult to determine the cause of a patient's malabsorption by history or physical examination, but it is desirable to make a specific diagnosis so that appropriate therapy can be initiated. If pancreatic insufficiency is suspected, it is important to confirm the diagnosis by objective testing. Many tests have been designed to assess pancreatic exocrine secretion; unfortunately, some of the traditional tests are difficult to carry out and the results often are misleading.[1-3] Therefore, any clinician who deals with malabsorptive disorders should understand which pancreatic function tests are available and how to best interpret the results. This review attempts to place into perspective the traditional pancreatic exocrine function tests and explore newer tests.

The pancreatic function tests described below are classified as direct or indirect. The direct tests measure pancreatic secretion in response to pharmacological or physiological stimulants, whereas the indirect tests assess pancreatic secretion by measuring its effect on ingested nutrients.

Direct Tests of Pancreatic Exocrine Function

The secretin stimulation and Lundh tests are the oldest and most studied of the pancreatic

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ABBREVIATIONS USED IN TEXT

BT-PABA = N-benzoyl-N-tyrosyl para-aminobenzoic acid
CCK = cholecystokinin
CO_2 = carbon dioxide
IF = intrinsic factor

exocrine function tests. In these tests one measures the volume of fluid, enzymes and bicarbonate secreted into the duodenum after a pancreatic stimulus. Another direct test of pancreatic secretion is the measurement of stool enzyme concentrations. The measurement of trypsin or isoamylase activity in serum also has been used to assess pancreatic function more or less directly.

Secretin Test

The stimulants of the pancreas used in the secretin test are intravenously injected gastrointestinal hormones.[4,5] Formerly, crude preparations of secretin were used for this purpose, but it was discovered that these contained cholecystokinin (CCK) as well as secretin. Secretin stimulates bicarbonate and water secretion by the pancreas, whereas CCK stimulates enzyme (protein) secretion. Now that essentially pure enzyme preparations are available, one can test separately for water and bicarbonate secretion, on the one hand, or enzyme secretion, on the other hand, depending on which hormone is used.[6,7] By simultaneously administering secretin and CCK, both kinds of secretory response can be measured. Different amounts of the hormones have been used alone or in various combinations, either as bolus injections or as continuous infusions, to determine the optimal dose for distinguishing normal from abnormal pancreatic function.[8,9] The best results have been reported with the use of submaximal doses of the hormones given by continuous infusion.[3]

The secretin test requires the passage of a triple lumen tube by mouth or nose into the stomach and duodenum, or a double lumen tube into the duodenum and a separate single lumen tube into the antrum of the stomach. The gastric tube is necessary for the removal of gastric acid and pepsin so that enzymes secreted into the duodenum will not be denatured. The first of the duodenal tubes is used for collecting duodenal content; its distal opening usually is placed near the angle of Treitz by fluoroscopic guidance. The second duodenal tube is used for the infusion of a nonabsorbable marker, such as polyethylene glycol or bromsulphalein[10]; the opening of this tube must be proximal enough to the collection port of the first tube so there will be adequate mixing of the marker substance with the pancreatic secretions before aspiration. The marker substance is introduced at a known concentration and rate. The concentrations of the marker, bicarbonate and enzymes in the collected duodenal juice are then determined, and from simple mathematical equations the output of pancreatic enzymes and bicarbonate can be calculated.[10,11] Before the nonabsorbable marker technique (which does not require the complete collection of duodenal juice) was used, incomplete collection was a major cause of erroneous results.

After a control period of infusion of the marker and aspiration of duodenal content (usually half an hour), the hormone is administered. If volume and bicarbonate production are to be measured, pure secretin from the Karolinska Institute in Sweden should be used (usual dose is 0.5 to 1.0 CU per kg of body weight per hour). The synthetic octapeptide of CCK sincalide (Kinevac), the active portion of the CCK molecule, is the most satisfactory and least expensive preparation available for the stimulation of pancreatic enzyme secretion. The usual dose of CCK is 50 μg per kg of body weight per hour administered by continuous infusion. Duodenal juice is collected by gravity drainage in iced tubes at 15-minute intervals for 1½ hours after the stimulants are given.

The secretin test has several drawbacks: (1) the length of the procedure, (2) the necessity for nasogastric intubation, which frequently is poorly tolerated by the patient and (3) radiation exposure during placement of the tube. Nevertheless, when careful attention is given to all procedural details, 90 percent accuracy in differentiating normal from abnormal pancreatic function can be attained.[4]

Lundh Test

In the Lundh test the stimulus to pancreatic secretion is a standardized liquid meal ingested by the patient after a tube has been passed into the duodenum.[12-14] The constituents of this meal cause the duodenum to secrete the hormones CCK and secretin, which in turn stimulate pancreatic secretion. The meal also distends the stomach, producing pancreatic secretion via nervous system reflexes. Even though this test sometimes is referred to as an indirect method of pancreatic stimulation, it is in fact the physiological way in

which the pancreas is stimulated. The effect of the stimulant (food) on enzyme and bicarbonate secretion is measured directly in the aspirated duodenal juice.

The Lundh test also requires duodenal intubation. Traditionally, a single lumen tube is placed so that its distal opening is near the angle of Treitz. The patient then drinks a 300-ml liquid meal (5 percent protein, 6 percent fat and 15 percent carbohydrate), and duodenal contents are aspirated at 15-minute intervals for two hours. The duodenal juice is assayed for bicarbonate and enzyme concentrations. The test can distinguish between normal and abnormal pancreatic function found in pancreatic cancer or pancreatic insufficiency with an accuracy of 75 percent to 90 percent, depending on the type of disease present (patients with pancreatic cancer may have normal or decreased outputs of enzymes and bicarbonate, depending on the location of the tumor).[14]

In the standard Lundh meal technique, because of uncertainty about completeness of duodenal aspiration and because a marker is not used, only enzyme concentrations rather than enzyme output can be determined. Furthermore, in comparison with the secretin test, there is an increased potential in the Lundh test for acid and pepsin to enter the duodenum, which might lead to more variable values for measured enzyme concentrations because of denaturation. Gastric acid entering the duodenum also prevents accurate measurement of bicarbonate secretion. Because the Lundh meal relies on endogenous hormones to stimulate pancreatic secretion, there are situations (for example, after Billroth II gastrectomy or in celiac disease) when test results may suggest decreased pancreatic exocrine function while actually indicating poor physiological stimulation of the pancreas.[15,16] Thus, the results may show an important pathological process but may be misinterpreted clinically.

The secretin test has stood the test of time. The use of nonabsorbable markers to enable quantitation of secretion has made the test reasonably reproducible and sensitive for quantitation of pancreatic exocrine function. However, the extent of its use is limited by its complexities. Ideally, the test should be done only by well-trained personnel who are familiar with tube placement, sample collection and enzyme assays. As a general rule, the test is indicated too infrequently to warrant its use outside of large, specialized centers.

The Lundh meal test is simpler and cheaper to do than is the secretin test, but it still requires nasogastric intubation, prolonged careful monitoring and the need for expert handling of the collected specimens. Because data produced by the Lundh test may be less accurate or more difficult to interpret, the secretin test is recommended as the best available direct test of pancreatic exocrine function.

Fecal Enzyme Assays

Because feces are relatively easy to obtain from patients, many workers have attempted to correlate pancreatic exocrine function with the concentration of enzymes present in stool specimens.[17,18] Measurement of chymotrypsin is the least variable, but the range of values obtained is so great that the test is not a reliable measure of pancreatic secretion and is no longer used in adults.

Serum Enzyme Assays

Serum amylase and lipase concentrations can be measured easily, but values do not correspond with the amount of pancreatic exocrine function. One study has reported decreased pancreatic isoamylase concentrations in the serum of patients with cystic fibrosis and pancreatic insufficiency, but at present this method has little clinical usefulness because of the difficulty in distinguishing pancreatic from salivary amylase.[19]

Trypsin is difficult to measure in serum because of the presence of inhibitors, but recently workers in England have developed a radioimmunoassay for serum trypsin. Although serum trypsin values are low in pancreatic insufficiency, they can also be low in chronic pancreatitis unassociated with exocrine insufficiency.[20,21] No improvement in distinguishing normal pancreatic function from pancreatic insufficiency has been achieved when serum trypsin is measured after food-induced stimulation of pancreatic secretion.[22] In summary, serum enzyme levels do not appear to be useful in diagnosing exocrine insufficiency.

Indirect Tests of Pancreatic Exocrine Function

Fat Absorption

Triglyceride absorption requires hydrolysis of the lipid by pancreatic lipase, solubilization by bile acids and uptake by epithelial cells of the small bowel mucosa. After absorption, some of the fatty acids are metabolized to carbon dioxide (CO_2) which is excreted through the lungs. Tri-

glyceride absorption can be quantitated by radioactive-labeled triglyceride tests. Initially, triolein, a triglyceride composed of glycerol and three molecules of the long-chain fatty acid oleate, was labeled with iodine 131.[23] The alteration of the triglyceride by iodination and in vitro and in vivo loss of the iodine 131 from the fatty acid resulted in a poor correlation between estimates of stool fat excretion and triolein I 131 absorption, and the test was abandoned. More recently, triglycerides labeled with carbon 14, such as triolein ^{14}C, tripalmitin ^{14}C and trioctanoin ^{14}C, have become available.[24-26] Absorption of ingested triolein ^{14}C (the ^{14}C is the carboxyl carbon on the oleic acid) can be easily assessed by measuring the appearance of $^{14}CO_2$ in the breath. The authors of a large study at the Mayo Clinic, who investigated the use of several fatty acids for detecting fat malabsorption, concluded that triolein ^{14}C was the most reliable agent for use in distinguishing normal nonobese patients from those with steatorrhea.[25] However, the accuracy of the radioactive-labeled triglyceride tests is compromised in patients who have altered fat metabolism (due to fever, hyperthyroidism, obesity or diabetes) or who are given glucose, which inhibits fat metabolism during the test.[27]

Carrying out a triolein ^{14}C breath test is simple. The patient ingests 5 μCi of triolein ^{14}C and 25 grams of Lipomul (emulsified corn oil) and then exhales into vials containing 1.0 mmole of Hyamine (a CO_2-trapping agent) in methanol. Each vial contains phenolphthalein, which turns from pink to colorless as the Hyamine is neutralized by combining with the exhaled CO_2; this color change signifies accurately when the CO_2 collection is complete. The peak of the radioactive excretion usually occurs within six hours from the time of ingestion of the triolein ^{14}C. The peak excretion has been shown to correlate best with the presence or absence of steatorrhea.

The triolein ^{14}C breath test cannot be used to differentiate fat malabsorption due to pancreatic insufficiency from that due to any other cause. In this respect the test is similar to the measurement of stool fat. Two modifications intended to make the test more specific for pancreatic disease have been described. In the first, the ratio of ^{14}C to ^{3}H in the serum is measured after the ingestion of the triglyceride labeled with carbon 14 and the fatty acid labeled with tritium (^{3}H).[28,29] Absorption of the fatty acid ^{14}C requires hydrolysis of the triglyceride ^{14}C by pancreatic lipase, whereas the fatty acid ^{3}H can be absorbed by the intestinal mucosa directly. Theoretically, the ^{14}C to ^{3}H ratio should be 1.0 or close to it if pancreatic function is normal. A decrease in the ratio suggests the presence of pancreatic insufficiency. By contrast, fat malabsorption secondary to a deficiency in bile acids or intestinal mucosal abnormalities impairs the absorption of the triglyceride ^{14}C and fatty acid ^{3}H about equally, leaving the ratio unaffected. Unfortunately, European studies using this method have not consistently distinguished normal pancreatic function from patients with pancreatic insufficiency.[28,29] The second modification of the triolein ^{14}C test is administration of triolein ^{14}C together with pancreatic extract to patients who have low $^{14}CO_2$ excretion values when the triolein ^{14}C is given alone.[30] Preliminary experience with this approach has been promising, although in a few patients with nonpancreatic malabsorption, a substantial increase in $^{14}CO_2$ excretion after ingestion of pancreatic extract was recorded.

At present, the triolein ^{14}C breath test appears to be about as sensitive and specific as the measurement of stool fat in the diagnosis of fat malabsorption. The time requirement of only 6 hours instead of 72 hours and the advantage of not having to collect or analyze stool are important points favoring use of the breath test.[25] The agents for doing the study are available, and the test can be set up in any hospital; however, it must be pointed out that most nuclear medicine departments do not routinely have the liquid scintillation spectrometers needed for detecting ^{14}C. The accuracy of the two-part tests in a large population still needs to be determined before it can be recommended as a routine method for detecting pancreatic insufficiency.

BT-PABA Test

N-benzoyl-N-tyrosyl para-aminobenzoic acid (BT-PABA) is the combination of para-aminobenzoic acid (PABA) and a chymotrypsin-sensitive dipeptide. When BT-PABA enters the duodenum the dipeptide is separated from the PABA by pancreatic chymotrypsin. The free PABA is readily absorbed and transported to the liver where it is conjugated. Most of the conjugated PABA is excreted into the urine where it can be measured by a simple colorimetric technique.

The BT-PABA test has been studied extensively in Europe, Japan and the United States.[31-35] Some reports have suggested that the test is 80 percent

sensitive and 90 percent specific for detecting pancreatic insufficiency or pancreatic cancer. However, results of the BT-PABA test do not always correlate with those of the secretin test, and values in groups of normal subjects and patients with pancreatic insufficiency often overlap. Several variables can influence the results of the BT-PABA test: (1) whether the BT-PABA is given with a liquid meal or alone, (2) the presence of abnormal small bowel mucosa, (3) the presence of cirrhosis, (4) the presence of abnormal renal function, (5) the acidity of the stomach and (6) ingestion by the patient of substances that can interfere with the assay for PABA, such as sulfonamides, thiazides, furosemide, acetaminophen, chloramphenicol, prunes or cranberries.[34,36] To circumvent these problems, a two-stage test has been devised.[37] On day one, free PABA (680 mg) is ingested by the patient, and PABA excreted in urine during the next 6 to 24 hours is measured. On the next day the patient ingests an equivalent amount of PABA as BT-PABA, and the excretion of PABA is compared with that of the first day. By determining the ratio of PABA excreted after administration of the two molecular forms, many of the variables mentioned above can be eliminated. Preliminary results with the test are encouraging. Further, it is easy to carry out and does not subject the patient to radiation exposure, thus making it safe for use in pregnant women and children.

Pancreatic Schilling Test

The most recently developed test of pancreatic exocrine function is based on new information about the absorption of cobalamin (vitamin B_{12}). The traditional model for cobalamin absorption includes intrinsic factor (IF) and the ileal mucosa: cobalamin binds to IF in the stomach, and the complex is absorbed across the terminal ileum. Recently, it has been discovered that another glycoprotein, R-protein, is present in gastric juice, bile and saliva.[38,39] R-protein in an acid environment binds cobalamin with a 150-fold higher affinity than does IF; in an alkaline environment, as in the normal duodenum, R-protein binding to cobalamin is only three times greater than IF binding. Pancreatic enzymes can partially degrade R-protein, thereby further reducing the ability of the glycoprotein to bind to cobalamin.[38] IF is resistant to pancreatic enzyme activity. Thus, a new model for cobalamin absorption has been proposed: Cobalamin binds to R-protein in the stomach; in the alkaline duodenum, with the aid of pancreatic enzymes, the cobalamin transfers to IF; the IF-cobalamin complex is then absorbed across the terminal ileum.[38-40] The transfer of cobalamin to IF is a necessary step because cobalamin bound to R-protein cannot be absorbed by the ileum.

This model is consistent with the well-recognized observation[41,42] that in as many as 50 percent of patients with pancreatic insufficiency, cobalamin is not absorbed normally.

The pancreatic Schilling test is based on the requirement for pancreatic enzymes in the absorption of cobalamin.[43] The test is carried out by simultaneously giving the patient ^{57}Co-cobalamin-IF, ^{58}Co-cobalamin-R-protein, cobinamide and IF by mouth. Cobinamide is an analogue of cobalamin that irreversibly binds to R-protein; it is given to prevent endogenous R-protein from disassociating the exogenous cobalamin ^{57}Co from IF. The free IF is given to assure that sufficient IF will be present to bind to the cobalamin ^{58}Co in the duodenum once the cobalamin has been released from R-protein by pancreatic enzymes. The patient also receives 1,000 μg of unlabeled cobalamin intramuscularly, as in the standard Schilling test, to saturate binding sites and, thereby, enhance urinary excretion of absorbed radioactive cobalamin. The patient collects his or her urine for 24 hours, and the radioactivity of the ^{57}Co and ^{58}Co in the urine is counted (both isotopes are gamma emitters but have different energy emission peaks) (Figure 1).

When this test was carried out on 26 healthy subjects at this institution, it was found that the ratio of ^{58}Co to ^{57}Co excreted in the urine was near 1.0. This result presumably reflects the similar absorption and excretion of cobalamin that occurs in the presence of a normally functioning pancreas irrespective of whether the cobalamin is bound to R-protein or to IF. In 15 patients with pancreatic insufficiency, the ratio of ^{58}Co to ^{57}Co excretion was much less than 1.0, presumably reflecting the decreased absorption of cobalamin ^{58}Co bound to R-protein that occurs when pancreatic proteases are deficient. There was no overlap of ratios in the normal group with those of the patients who had pancreatic insufficiency. Pancreatic insufficiency was confirmed in all the patients by the secretin test, and none of the normal subjects had steatorrhea.

If further studies confirm the findings of this initial investigation, the pancreatic Schilling test

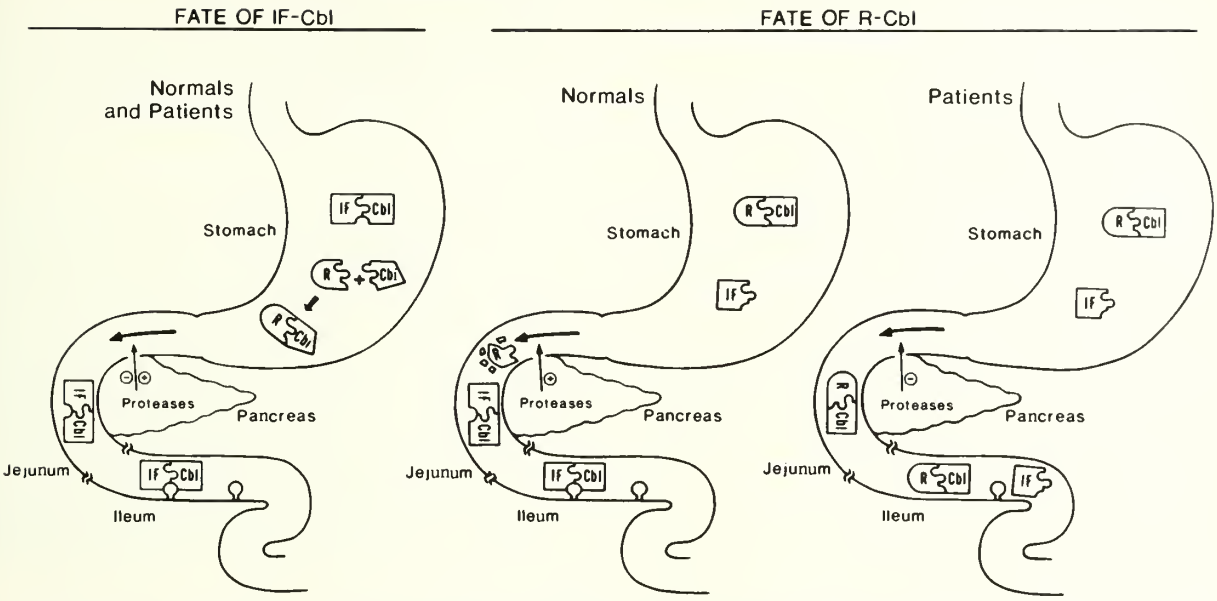

Figure 1.—A model of the dual-label pancreatic Schilling test. The drawing on the left (under fate of IF-Cbl) illustrates how cobalamin (Cbl) bound to IF (intrinsic factor) is handled in normal subjects and in patients with pancreatic insufficiency. The IF-Cbl passes through the gut and is absorbed in the terminal ileum regardless of pancreatic function. Note that R-protein (R) is prevented from interacting with the IF-Cbl by cobinamide (Cbl), a cobalamin analogue with a higher affinity for R-proteiin than cobalamin. The other two drawings illustrate the different handling of cobalamin bound to R-protein (R-Cbl) in both normal subjects and patients. In normal persons R-protein must be degraded by pancreatic enzymes before the cobalamin can be bound to intrinsic factor and transported to the ileum for absorption. However, in patients with decreased pancreatic exocrine function the R-protein remains bound to the cobalamin and cannot be absorbed by the terminal ileum. Thus, if IF-Cbl and R-Cbl are labeled with different isotopes, the differential handling can be easily detected by collecting the patient's urine.

may prove to be the most accurate indirect test of pancreatic exocrine function available. The use of the excretion ratio of ^{58}Co to ^{57}Co eliminates false-positive results created by abnormal absorption of cobalamin secondary to intestinal mucosal disease, by abnormal excretion because of renal insufficiency or by incomplete collection of urine because each of these factors affects the excretion of cobalamin ^{58}Co and cobalamin ^{57}Co equally, leaving the ratio unchanged. In the future the ability to provide all the ingested ingredients as capsules will make the test technically similar to the dual-labeled Schilling tests used at present. Thus, any nuclear medicine department should be able to do the pancreatic Schilling test.

Conclusion

Among the available tests of pancreatic exocrine function, the secretin test is the most accurate, provided that it is done carefully by well-trained personnel. Triolein ^{14}C is available, but not enough data have been accumulated on the modifications described above to advocate that this test can be used for routine detection of pancreatic insufficiency. Moreover, many hospitals do not have the proper equipment for carrying it out. The pancreatic Schilling test may be the simplest and most reliable, but it is not yet commercially available. The BT-PABA test will soon be available in this country, and I expect that it will be one of the indirect tests of pancreatic function most widely accepted for clinical use in the near future. This will be especially beneficial to smaller, community hospitals that do not now have the facilities required for reliably conducting the complicated secretin stimulation test.

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Pathophysiological Conference

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Refer to: Olerud JE, Robertson HT, Hossack KF, et al: A patient with polycythemia. University of Washington School of Medicine (Pathophysiological Conference). West J Med 135:375-382, Nov 1981

A Patient With Polycythemia

Case Presentation

THE PATIENT, a 56-year-old man of Finnish descent, had a ten-year history of polycythemia. In 1969, following an illness diagnosed as "Asiatic flu," he experienced fatigue and recurrent epistaxis, the latter finally stopped by cautery treatment. He had previously had occasional nosebleeds, perhaps three or four times a year, but at no time were they severe. In 1970 a routine blood study showed a hematocrit of 66. After initial phlebotomies in March 1971 he was referred to a diagnostic clinic, where it was noted that he also had pruritis. In a blood volume determination, the "red cell mass" of 47 ml of erythrocytes per kg of body weight was noted; bone marrow showed erythroid hyperplasia and blood uric acid levels were elevated. An excretory urogram showed no abnormalities. The only additional finding was an immune globulin spike of about 1 gram, which was considered to be a benign gammopathy. A diagnosis of polycythemia vera was made.

Because of the frequency with which phlebotomy was required, in December of the following year he was given pipobroman (Vercyte) at a dose of 100 mg a day to control erythrocyte production. After eight months of treatment, bone marrow suppression occurred and the drug was stopped. During the next four months some 14 units of packed erythrocytes were transfused to support his circulating hemoglobin. He was referred to the University Hospital in January of 1974, at which time hematocrit was 20, platelet count 60,000 and leukocyte count 3,100 per cu mm. On physical examination, in addition to pallor, numerous focal vascular lesions up to 1 or 2 cm in diameter were noted. These were distributed over the trunk; a hemangioma over the left scapula was noted as well. The patient was not certain but suggested the lesions had been present for only a year or two. There was no family history of similar vascular lesions, and examination of his two sons and mother showed no abnormalities. The patient's spleen and liver were not enlarged on physical examination. There was Bromsulphalein (BSP) retention of 19 percent. His marrow hypofunction was attributed to pipobroman therapy, and the question was raised as to whether this drug was also responsible for the liver dysfunction and vascular lesions.

Fluoxymesterone (Halotestin) therapy, 120 mg per day, was begun, and his marrow function improved during the following four months to the extent that his polycythemia returned, although his platelet count subsequently remained at about 100,000 and leukocyte count at about 4,000 per cu mm. Between 1974 and 1979 the patient's hematocrit was held in the low 50's by phlebotomy, but his exercise tolerance decreased to the point that in early 1979 he discontinued his daily three-mile run because of dyspnea and fatigue. On the suspicion that severe iron deficiency produced by phlebotomy was in part responsible for these

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ABBREVIATIONS USED IN TEXT

Pa_{O_2} = partial pressure of oxygen (arterial)
P_{O_2} = partial pressure of oxygen
P_{50} = partial pressure of oxygen at which hemoglobin is half saturated with oxygen

TABLE 1.—*Pulmonary Function Studies (August 1979)*

	Measured	*Predicted (percent of normal)*
Vital capacity (liters)	5.3	120
Total lung capacity (liters)	8.4	124
Forced expired volume in one second (FEV_1) (liters)	4.3	123
Diffusing capacity (ml/min-mm of mercury) (single breath, corrected to Hb of 15 grams per dl)	29.3	112
Alveolar gas uniformity (percent) (ΔN_2 per 500 ml)	0.5	(normal<1.0)

Hb = hemoglobin; ΔN_2 = changes in nitrogen distribution.

symptoms, therapeutic doses of iron were given, which resulted in a substantial increase in the amount of bleeding required to control his hematocrit; some 17 phlebotomies were done in the six months preceding admission.

He returned to the University Hospital in 1979 for evaluation of his persistent polycythemia and fatigue. On that admission the large number of spider-like vascular lesions over his upper thorax seemed increasingly prominent. A few lesions were also present on his lips and hands. Nasal and oral mucous membranes were minimally involved. Examination of the heart showed a basilar systolic murmur. There were no diastolic murmurs or gallops, and a jugular venous pressure was normal. Examination of the lungs showed no abnormalities. The spleen was not palpable, the liver dullness to percussion was 14 cm at the midclavicular line and no abnormal masses were palpable in the abdomen. The fingernails were slightly curved, with softened nail beds.

Laboratory studies showed the following: hematocrit 64, leukocyte count 4,600 and platelet count 109,000 per cu mm. Blood chemistry values were normal except for bicarbonate concentrations, which varied between 13 and 16 mEq per liter on several determinations. The anion gap, blood urea nitrogen and creatinine values and findings on analysis of urine were all within normal limits. Standard posteroanterior roentgenograms of the chest showed no abnormalities. An electrocardiogram showed sinus rhythm and left atrial and ventricular hypertrophy. Echocardiography suggested a moderate degree of aortic stenosis. Pulmonary function test findings (Table 1) were normal. Arterial blood gas values were as follows: partial pressure of oxygen (P_{O_2}) 62 mm of mercury, calculated arterial oxygen saturation 93 percent, partial pressure of carbon dioxide 26 mm of mercury and pH 7.41. Arterial saturation at night was monitored during sleep with an ear oximeter and found to be stable at between 87 percent and 89 percent saturation. Because of progressive exertional symptoms and documentation of aortic stenosis by catheterization, a prosthetic aortic valve was implanted at the patient's community hospital in November 1979. His exercise tolerance did not improve. In April 1980 further studies were carried out as indicated by the following consultations to evaluate the cause of the patient's polycythemia.

Hematology Consultation

CLEMENT A. FINCH, MD,* and
WARREN D. BOWMAN, Jr, MD†

THIS PATIENT was originally seen in 1974 when his marrow function was suppressed, presumably by the alkalating agent pipobroman. His polycythemia, however, returned and was investigated in 1979. At that time there were several findings that indicated a need to reevaluate the original diagnosis of polycythemia vera. There was no evidence of excessive granulopoiesis or thrombopoiesis, and there was no splenomegaly. The continued suppression of granulocytes and platelets from prior chemotherapy at a time when there was excessive proliferation of erythrocytes seemed atypical for polycythemia vera (where the affected cell clone is expected to have a greater than normal sensitivity to myelosuppressive agents). More important, the patient's vascular lesions and progressive hypoxia suggested another cause of the polycythemia.

In approaching the diagnosis of polycythemia systematically (Figure 1), the previous blood volume determination was helpful. The value of 47 ml of erythrocytes per kg of body weight excluded a hypovolemic type of polycythemia (stress

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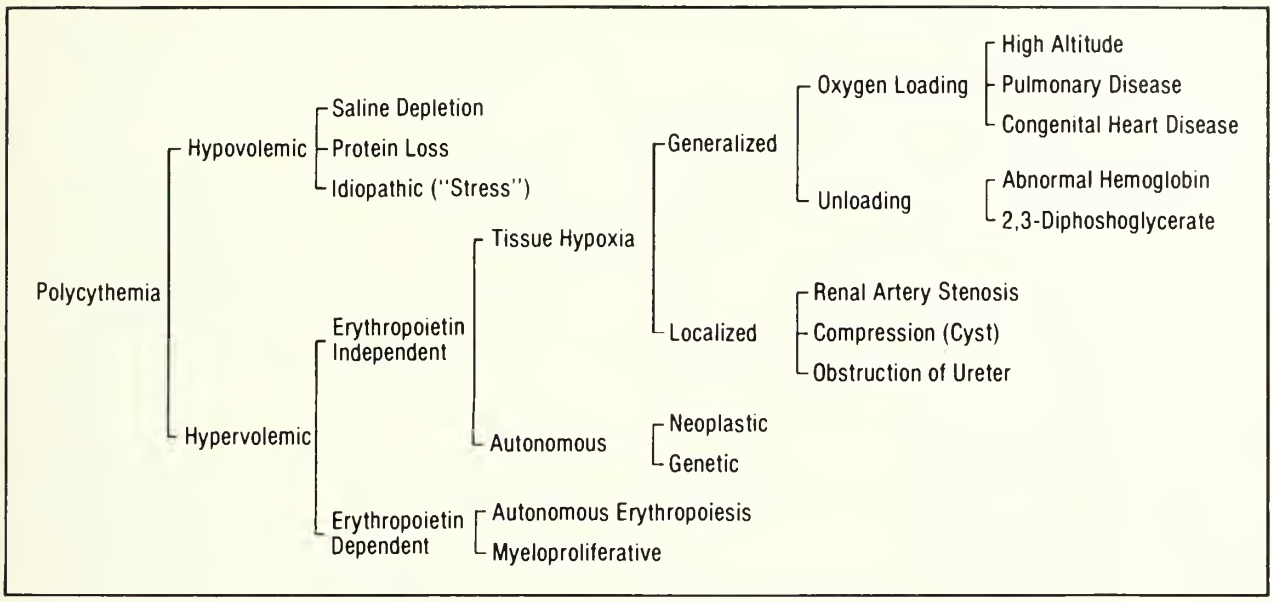

Figure 1.—Diagnostic approach to polycythemia.

polycythemia), although this would seem unlikely anyway in view of the severity and duration of the condition.[1] The next major question was whether the polycythemia was erythropoietin-induced or whether it was the result of autonomous activity of the erythroid marrow (polycythemia vera). Here the essential measurement was that of plasma or urinary erythropoietin at the patient's elevated hematocrit level.[2] A bioassay of the patient's plasma carried out by Dr. John Adamson (Chief of Hematology Section, Veterans Administration Medical Center, Seattle, Washington, Oct. 12, 1979) in polycythemic mice showed an incorporation of radioactive iron by erythrocytes of 17.8 ± 7.0 percent (controls 0.5 or 1.0 percent), indicating an erythropoietin level far above normal. This excluded polycythemia vera because erythropoietin output is suppressed in this condition.[3] The elevated erythropoietin could have been a result of hypoxia or an inappropriately high erythropoietin output. While distinction between these categories could probably have been made by following erythropoietin levels as the hematocrit was reduced by phlebotomy, a number of indicators of hypoxia had already been observed. There was mild clubbing of the fingers, an arterial oxygen saturation measured by ear oximeter of 89 percent and a decrease in carbon dioxide-combining power. To exclude an abnormality in erythrocyte metabolism (2,3-diphosphoglycerate) or an abnormal hemoglobin with a high affinity for oxygen,[4] the oxygen pressure required to half saturate the patient's hemoglobin in vitro (P_{50}) was determined and found to be 30.8 mm of mercury as compared with the normal value of 26.7 mm of mercury. Using the measured P_{50} to calculate a saturation for the original Po_2 determination of 62 mm of mercury, the calculated oxygen saturation was 89 percent. Further studies were undertaken to evaluate the progressive arterial deoxygenation.

Pulmonary Consultation

H. THOMAS ROBERTSON, MD*

At the time of admission in August 1979, the hypoxemia observed did not seem sufficient to have accounted for the long history of polycythemia. Generally, the arterial partial pressure of oxygen (Pao_2) must remain below 50 mm of mercury to induce polycythemia of the degree observed in this patient. However, a substantial abnormality in oxygenation was present, masked by compensatory hyperventilation. Using the alveolar gas equation, an alveolar-arterial oxygen difference of 48 mm of mercury was present, as contrasted to the normal value of less than 20 mm of mercury. This increase could be caused by pulmonary or cardiac shunts, ventilation-perfusion mismatching in the lungs or oxygen diffusion limitation, although from recent studies, the latter

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mechanism has not been thought to be clinically significant.[5] After breathing 100 percent oxygen for 15 minutes, the patient's Pa_{O_2} value returned to normal range (Table 2). This finding suggested that hypoxemia was a result of a severe ventilation-perfusion mismatch rather than shunt, where desaturation would be only minimally improved by breathing 100 percent oxygen. Ventilation-perfusion abnormalities of this severity ordinarily are accompanied by severe airway obstruction and gas maldistribution. Because these findings were not observed (Table 1), a second study was undertaken to evaluate further the possibility of intrapulmonary shunting. Arteriovenous shunts within the lung are held open during full inspiration, whereas the normal alveolar microvasculature is compressed; the reverse occurs during full expiration.[6] When this simple test was done, the patient was found to have the lowest Pa_{O_2} while breathing 100 percent oxygen during inspiration, and the highest Pa_{O_2} during expiration (Table 3). We therefore reconsidered the possibility of an intrapulmonary shunt.

Exercise studies were done to evaluate the patient's complaint of dyspnea (Table 4). The limiting element in exercise performance can usually be identified by means of electrocardiographic findings, expired gas volumes and concentrations, and arterial blood gas determinations.[7] The patient showed a significant limitation in maximal exercise capacity—the oxygen volume uptake was 18 ml per kg of body weight per minute as compared to normal values of 30 to 35 ml—accompanied by a modest tachycardia but substantial hyperventilation. Within one minute at 100 kpm on the cycle ergometer, a level of exercise comparable to a slow walk on level ground, the arterial oxygen saturation dropped from 88 percent to 81 percent. This degree of exertional hypoxia provided an adequate explanation for the serious dyspnea and the polycythemia.

TABLE 2.—*Arterial Blood Gas Determinations*

	Date of Test		
	8/79	*4/80*	*4/80*
Oxygen concentration of inspired air (percent)	21	21	100
Pa_{O_2} (mm of mercury)	62	50	558
Pa_{CO_2} (mm of mercury)	26	28	28
pH	7.41	7.39	7.39
Bicarbonate (mEq/liter)	16	16	16
Oxygen saturation of hemoglobin (percent)*	88.8	78.9	99.9

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial).

*Corrected for high P_{50}. (P_{50} = partial pressure of oxygen at which hemoglobin is half-saturated with oxygen.)

TABLE 3.—*Testing for Intrapulmonary Shunt*

Inspired Oxygen Concentration (percent) Breathing Maneuver	*21 Tidal Breathing*	*100 Tidal Breathing*	*100 Held Inspiration*	*100 Held Expiration*
Pa_{O_2} (mm of mercury)	48	467	438	497
Pa_{CO_2} (mm of mercury)	29	29	29	30
pH	7.45	7.44	7.46	7.44

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial).

TABLE 4.—*Work Exercise Test*

	Load (kpm/minute)				
	Rest	*100*	*300*	*500*	*700*
Pa_{O_2} (mm of mercury)	60	48	47	46	44
Pa_{CO_2} (mm of mercury)	31	30	29	29	28
pH	7.40	7.40	7.40	7.39	7.37
$\dot{V}_{O_2}$ (liters/min)	0.338	0.513	0.751	1.01	1.25
$\dot{V}_E$ (liters/min)	27	37	53	72	101

Pa_{CO_2} = partial pressure of carbon dioxide (arterial); Pa_{O_2} = partial pressure of oxygen (arterial); $\dot{V}_E$ = minute ventilation; $\dot{V}_{O_2}$ = oxygen consumption.

Nuclear Medicine Consultation

WIL B. NELP, MD*

RADIONUCLIDE PERFUSION-DISTRIBUTION studies were done to verify the presence and the amount of pulmonary-to-systemic shunting. The patient received an antecubital intravenous injection of technetium 99m macroaggregated albumin. The injection contained 0.5 to 1.0×10^6 particles, with a mean particle size of 40μ—sufficiently large for trapping in the first capillary bed encountered. This study, carried out while the patient was resting (Figure 2A), showed the expected pulmonary perfusion pattern in the lungs, but also showed significant shunting of particles, with labeling of tissues of the systemic circulation. In the anterior view (Figure 2A), one can see most clearly the flow to the brain and abdominal organs. By total body imaging immediately following injection and computer analysis, it was estimated that approximately 80 percent of the injected activity was deposited in the lungs, while 20 percent of the activity bypassed the pulmonary circuit to enter the systemic circulation.

Two days later the study was repeated (Figure

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Figure 2.—Anterior gamma camera whole-body perfusion images following intravenous injection of technetium 99m macroaggregated albumin. **Figure 2A** shows shunting through legs to viscera and central nervous system following injection of medium with the patient in a resting position. **Figure 2B** shows the flow pattern following injection at peak exercise, with prominent shunting to muscles.

2B), this time when the patient had achieved maximum exercise on a bicycle ergometer (10.5 minutes at 400 kpm per minute). The estimated systemic shunt increased to 30 percent, and there was a major shift in the distribution of the systemic flow pattern because of the exercise. Note the substantial increase in relative flow to the leg muscles and a relative decrease in the cerebral and visceral components.

The macroaggregated, albumin-distribution studies confirmed the presence of a significant pulmonary-to-systemic shunt and suggested that the degree of shunting was increased during exercise. This latter finding was consistent with the patient's symptoms and pulmonary studies carried out during exercise. Detailed imaging of the lung perfusion pattern did not indicate exactly where the shunt was. In addition, a xenon 133 ventilation study gave normal results during inspiration, at equilibrium and in washout phases.

Cardiology Consultation

KENNETH F. HOSSACK, MD*

THE LONG HISTORY of increased erythrocyte production in this patient without overt arterial desaturation contributed to the difficulty in identifying the underlying pathological condition. In general, cardiovascular problems associated with secondary polycythemia in this age group suggest an intracardiac shunt with reversal of flow due to pulmonary hypertension. The latter is a reaction of the pulmonary vasculature to the initial increased pulmonary blood flow.[8] In the fifth and sixth decades of life, an atrial septal defect is the most common condition associated with this type of abnormal pathophysiology. Rarely patients with a patent ductus arteriosus or a ventricular septal defect may survive into their sixth decade. There are case reports of rare congenital abnormalities associated with intracardiac right-to-left shunting, and these include tetralogy of Fallot, ventricular septal defect associated with pulmonary stenosis and certain types of corrected transposition. In this patient there were no physical findings or electrocardiographic signs to support a diagnosis of pulmonary hypertension. Both the roentgenogram of the chest and the echocardiogram showed normal cardiac configuration, thus making intracardiac shunting extremely unlikely. This left an intrapulmonary abnormality as a more likely cause for the right-to-left shunt.

Catheterization was done to quantitate the right-to-left shunt and to locate an anatomic area of shunting. The likelihood of finding localized areas available for surgical resection seemed remote in view of the normal findings on the roentgenogram of the chest. Previously reported case histories of intrapulmonary right-to-left shunting usually have been associated with pronounced abnormalities shown on plane x-ray studies.[9-11] In Table 5 the hemodynamic and the oxygen content data obtained at the time of catheterization are presented. All the right-sided cardiac pressures were within normal limits. A peak systolic gradient of 34 mm of mercury across the aortic valve prosthesis was measured. The systemic blood flow was 7.4 liters per minute (cardiac index is 4.1 liters per minute per sq m). The effective pulmo-

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TABLE 5.—*Hemodynamic Studies*

	Pressure (mm of mercury)		Blood Oxygen Content (vol per dl)
	Phasic	Mean	
Site			
Superior vena cava	..	..	13.5
Inferior vena cava	..	..	13.0
Right atrium	..	8	13.1
Right ventricle	30/7	..	12.7
Pulmonary artery	30/15	18	12.8
Pulmonary capillary	..	12	..
Left ventricle	149/10	..	..
Aorta	110/68	84	16.6

Oxygen content data

Oxygen consumption = 281 ml/min

$$\text{Effective pulmonary flow} = \frac{281}{(18.7-12.8)\ 10} = 5.3 \text{ liters/min}$$

$$\text{Systemic flow} = \frac{281}{(16.6-12.8)\ 10} = 7.4 \text{ liters/min}$$

Right-to-left shunt: 7.4 − 5.3 = 2.1 liters/min

nary blood flow was calculated assuming a 97 percent saturation of pulmonary capillary blood. This value was 5.3 liters per minute, with a right-to-left shunt of 2.1 liters per minute. Selective pulmonary angiography was done and this showed multiple small areas of increased blood flow consistent with arteriovenous malformations. No discrete large fistula was seen, consistent with normal findings on the roentgenogram of the chest. Similar negative x-ray findings have been reported to occur[11,12] but are rare.

Dermatology Consultation

JOHN E. OLERUD, MD, and
GEORGE F. ODLAND, MD*

THE PATIENT had a blood vessel dysplasia involving primarily the skin of the trunk (Figure 3A and B) and the lungs. The typical vascular lesion was a pulsating spider angioma (Figure 3C). In addition, a large vascular nevus seen on the back was thought to be a port-wine stain in which a nodular component had developed with advancing age. Although several aspects of the clinical presentation were atypical, it seemed possible that this patient's disorder represented a variant of hereditary hemorrhagic telangiectasia. Osler, in his classic description of that syndrome, characterized three types of cutaneous lesions.[13] They included pinpoint angiomas, spider angiomas (which he felt were the most common) and the nodular or split-pea variety, which he thought might arise from the spider form. In a meticulous study of skin lesions in more than 100 patients with hereditary hemorrhagic telangiectasia, Bean concluded that the characteristic lesion was a pinpoint angioma.[14] When spider-like lesions were present, Bean felt that they often could be clinically differentiated from the vascular spiders seen in pregnancy and cirrhosis by the relatively large body and short legs forming the "spider" in hereditary hemorrhagic telangiectasia.

Epistaxis is the most frequent symptom in hereditary hemorrhagic telangiectasia. It occurs in 90 percent of patients, frequently resulting in iron deficiency and often requiring transfusion.[15] Arteriovenous fistulae of the lungs are relatively common and are usually visible on x-ray studies. They have been diagnosed in 15 percent and 23 percent, respectively, of patients with hereditary hemorrhagic telangiectasia from two large kindreds.[10,16] Telangiectasia and vascular malformations have been reported to involve the brain, spinal cord,[17] retina,[18] heart, spleen, intestine, liver[19] and a variety of other tissues. The family history is positive in 70 percent to 85 percent of the cases,[20-22] and the disease characteristically becomes manifest in the third decade of life.

This patient had several features that were atypical for familial hemorrhagic telangiectasia, in addition to an apparently negative family history. Except for a single three-month episode of epistaxis, the patient had not had unusual bleeding and his iron deficiency was attributable to the many phlebotomies. The distribution of this patient's lesions was predominantly over the trunk as opposed to the usual distribution (in a decreasing frequency) of face, lips, nares, tongue and hands.[23] The vascular lesions themselves more closely resembled tiny arteriovenous fistulae rather than the defective venules usually seen. Many of the lesions had a central arteriole that was elevated and pulsated vigorously. Thus, the essential feature of this patient's vascular dysplasia appeared to represent primarily many minute arteriovenous fistulae present in both the skin and the pulmonary vasculature.

Skin biopsy and cutaneous blood flow studies were done in an attempt to clarify further the anatomy and physiology of these lesions. Blood flow studies were carried out by Dr. Allen Holloway (Research Assistant Professor, Center for

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Figure 3.—Cutaneous involvement with vascular lesions is shown in **Figures 3A and B.** The large nevus on the left scapula is thought to represent a port-wine stain, in which nodular changes have developed with advancing age. **Figure 3C** shows a characteristic spider-like lesion with an elevated pulsatile center.

Bioengineering, University of Washington, Apr. 22, 1980), using a laser Doppler instrument.[24] A very high arterial blood flow was found in the center of the spider lesions, with a rapid decrease in flow in the legs. The flow in the center of the lesion was higher than could be measured by the laser Doppler instrument. Rough calculations using estimates of flow rates, vessel diameters and the number of spider-like lesions suggested that they could contribute to the high normal systemic flow.

Ultrastructure studies by Hashimoto and Pritzker[25] and by Menefee and co-workers[26] in familial hemorrhagic telangiectasia indicate that small tortuous vessels in the uppermost layer of the dermis have the morphology of a postcapillary venule and describe irregular fibrotic thickening of the wall of some vessels as well as replication of the basal laminae. Nödl's[27] description indicates that in the middermis there are vessels with thick hemilunar muscular coats, continuous with the dilated thin-walled vessels, suggesting arteriovenous anastomosis. A biopsy specimen of a vascular spider from this patient showed linear vessels extending for some distance through the dermis parallel to the surface, near the junction between the papillary and reticular dermis. These vessels had thin endothelial walls, large lumina, an irregular diameter and a uniform thickened and cellular wall suggesting perivascular fibrosis. A perforating "feeder" vessel was not identified. The changes seen were generally similar to those of familial hemorrhagic telangiectasia as previously described.

Summary

The differential diagnosis of polycythemia continues to present difficulties. An initial diagnosis of polycythemia vera based solely on an increase in erythrocytes without increases in leukocytes and platelets will frequently be wrong unless erythropoietin is also shown to be suppressed. Only with time and with increased exertional dyspnea was hypoxia considered in this patient, and the extent of hypoxia was not appreciated until studies were carried out during exercise. Vascular lesions on the thorax, later found to exist in the lungs as well, consisted of multiple arteriovenous aneurysms differing from the typical vascular lesions found in familial telangiectasia. The pulmonary lesions responsible for hypoxia were not apparent on ordinary radiographs and their physiological behavior was most unusual; tiny anatomic shunts could be partially oxygenated by high inspired oxygen concentrations. From a clinical standpoint, the polycythemia overshadowed the obscure hypoxia-producing pulmonary lesions. This case emphasizes the need for a physiological approach to the diagnosis of polycythemia.

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Information for Physicians and Patients About DES

FOUR PUBLICATIONS related to diethylstilbestrol (DES) exposure in utero are available without cost from the National Cancer Institute. Two of the publications are for health professionals: *Information for Physicians* and an illustrated *Atlas of Findings*. Two updated and expanded pamphlets for distribution to patients or the public also are available: *Questions and Answers About DES Exposure During Pregnancy and Before Birth* and *Were You or Your Daughter or Son Born After 1940?*

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Refer to: Ganem D: Toxic shock syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 135:383-388, Nov 1981

Toxic Shock Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *Despite the scrutiny of astute physicians over many years, new clinical entities continue to be recognized. Examples can be found in every discipline of medicine and include legionnaires' disease, pseudomembranous colitis, glucagonoma, eosinophilic fasciitis (Shulman's syndrome), idiopathic hypertrophic subaortic stenosis and primary hyperaldosteronism. Obviously, there is still scope for inquiring physicians to make a contribution to medical progress. Among the newly identified syndromes is the toxic shock syndrome, which has recently received much attention in medical publications and the popular press. For this Grand Rounds we have asked Dr. Donald Ganem to review this syndrome.*

DR. GANEM:† The first report identifying toxic shock syndrome (TSS) as a discrete nosologic entity was that of Todd and his colleagues in 1978.[1] They described a severe acute illness characterized by fever, profound hypotension and a scarlatiniform rash with subsequent desquamation in a group of seven children between 8 and 17 years of age. In many of the affected children, oliguria and azotemia developed, and there was laboratory evidence of disseminated intravascular coagulation. Most also had pronounced mucosal hyperemia, abdominal discomfort and watery diarrhea; one child died. Although blood cultures were negative in all cases, five of the patients had either colonization (upper respiratory or vaginal) or overt infection (of soft tissue or pleural space) with *Staphylococcus aureus*. Because of the similarity of some aspects of the clinical syndrome to known exotoxin-induced diseases (such as scarlet fever and staphylococcal scalded-skin syndrome), and because of the frequent recovery of *S aureus*, the authors postulated that the disease was a result of systemic absorption of a locally produced staphylococcal exotoxin, and so named the disease toxic shock syndrome. In support of this hypothesis, they reported that all five of their *S aureus* isolates elaborated a heat-labile epidermal toxin that could be demonstrated by inoculation of neonatal mice. Although subsequent studies have shown that this particular toxin is not unique to TSS-related strains (see below), most experts continue to accept the pathogenesis as proposed by Todd and co-workers,[1] and hence the syndrome still bears its original name.

The first clear description of TSS was thus not in menstruating females, the group that has since come to be so closely associated with the disease, but in young children (of both sexes). In a sense, this was fortunate because the presence of overt staphylococcal infection in some of these children made obvious the causative relationship of the

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ABBREVIATIONS USED IN TEXT
CDC = Centers for Disease Control
TSS = toxic shock syndrome

disease to *S aureus*. Such a relationship might have been less obvious had one merely to rely on the association between the clinical syndrome and the recovery of *S aureus* from the complex microbial environment of the vagina.

It is unlikely that TSS is an entirely new disease, although there are sound reasons to believe that its incidence has greatly increased in recent years. In retrospect, several published cases[2-4] of so-called staphylococcal scarlet fever may in fact have represented TSS. More recent reports of Kawasaki disease occurring in adults[5-7] are almost surely bona fide examples of TSS. Nevertheless, it remains true that before 1979, reports of TSS-like illnesses were extremely rare. However, beginning in late 1979, physicians in several state health departments[8] began receiving increasing numbers of reports of a severe illness occurring in young women, again characterized by high fever, abdominal complaints, myalgias, diffuse macular erythema and (often) refractory hypotension. Virtually all women (95 percent) had onset of symptoms during menses.[8] These reports were forwarded to the Centers for Disease Control (CDC), which has since maintained a national surveillance system. Figure 1 illustrates the major rise in the number of TSS cases reported to the CDC between 1979 and 1980.[9] It is unlikely that this increase was due solely to failure of physicians to recognize or report the condition in the past. Analysis of the reports by region indicated that cases were appearing throughout the country, without major concentration in any one locale. Similar cases were also reported in Canada,[10] Western Europe and Scandinavia.[9] In the ensuing

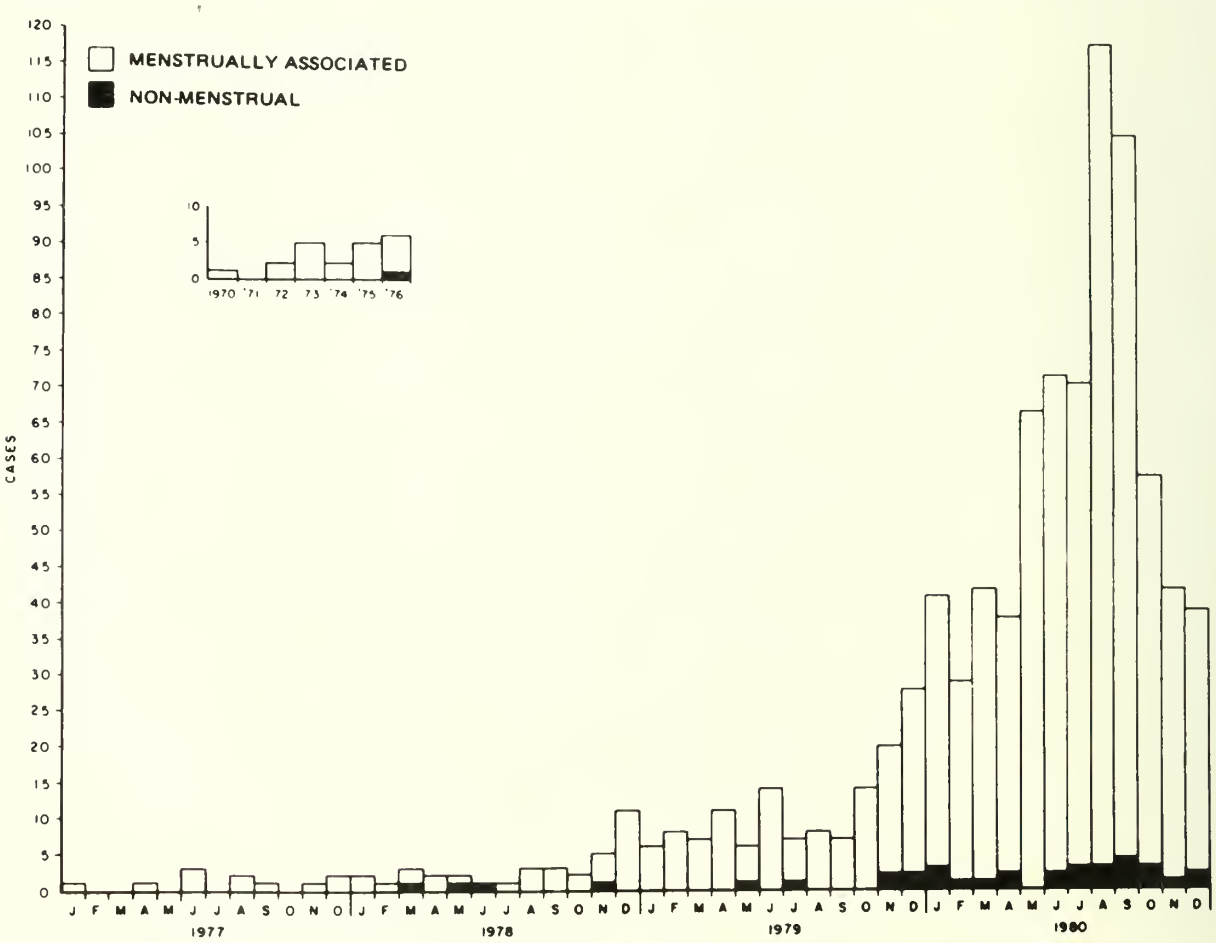

Figure 1.—Reported cases of toxic shock syndrome, by date of onset, in the United States, January 1970 through December 1980. The case definition requires four major criteria (fever, hypotension, rash and desquamation), involvement of three organ systems and absence of evidence for other causes. (Reprinted with permission from Centers for Disease Control and Morbidity Mortality Weekly Rep 30:25, Jan 30, 1981.)

sections we shall consider the clinical and epidemiologic features of TSS, with particular emphasis on their relation to its cause and pathogenesis.

Clinical Presentations

In early 1980, investigators at the CDC[11-13] and the Wisconsin State Health Department[14] initiated case-control studies of TSS to characterize better its clinical course and to attempt to identify risk factors for its acquisition. Central to this undertaking was the establishment of a rigorous case definition, to be certain that all included cases were indeed examples of the same illness. The criteria for inclusion in the CDC study[9] are given in Table 1 and are virtually identical to those used by other investigators.[14,15] In addition to the findings of fever, scarlatiniform rash and desquamation, the CDC required the presence of hypotension and involvement of at least three extracutaneous organ systems for inclusion.

These entry criteria ensure uniformity of disease and, thus, make possible meaningful assessment of risk factors. However, they also preselect a group of severely affected patients and, thus, may depict only one end of a spectrum of clinical presentations. Indeed, as experience with this entity grows, less severe forms are being recognized with increasing frequency.[16] It is important to realize that, for precisely this reason, these criteria were not intended to be diagnostic commandments for use in daily practice. Nevertheless, they do allow description of many of the varied clinical manifestations of this remarkable syndrome. Most obvious is the rash, which is macular, erythematous, blanches on pressure and is nonpruritic. Characteristically, desquamation, which is most pronounced over the palms and soles, occurs during convalescence. In this regard, the lesions are like those of Kawasaki disease and, of course, of scarlet fever. Rarely, hair and nail loss have been reported.

Gastrointestinal involvement is often pronounced, with diffuse abdominal pain, vomiting and (especially) diarrhea being commonly reported.[13-15,17] The latter is usually watery, without blood or fecal leukocytes being evident. Prominent mucous membrane involvement is frequent, with conjunctival, pharyngeal and vaginal hyperemia the usual findings. Patients often complain of pronounced musculoskeletal pains, most typically myalgias. These can involve the muscles of the abdominal wall, giving rise to abdominal tenderness. Perhaps most important of all the extracutaneous findings, however, is renal involvement, which can present in many forms. At one extreme is acute renal failure, with azotemia and oliguria, often occurring in combination with profound hypotension. Even in the absence of hypotension, however, other abnormalities, including pyuria and hematuria, can be observed; these are *not* related to direct infection of the urinary tract by the staphylococci. Neurologically, transient encephalopathic changes characterized by altered or depressed mentation, disproportionate to the degree of fever or hypotension, are often observed. Again, examination of cerebrospinal fluid documents that these symptoms are not the result of direct bacterial invasion of the central nervous system.[12]

Laboratory abnormalities are numerous but generally nonspecific. Leukocytosis and moderate thrombocytopenia are common, as are mildly elevated serum transaminase levels. Azotemia, hematuria and pyuria have already been mentioned above. Two other laboratory findings are of note. About 40 percent of severely ill patients

TABLE 1.—*Toxic Shock Syndrome Case Definition**

Fever (temperature $\geq$38.9°C [102°F]).

Rash (diffuse macular erythroderma).

Desquamation, one to two weeks after onset of illness, particularly of palms and soles.

Hypotension (systolic blood pressure $\leq$90 mm of mercury for adults or $<$5th percentile by age for children 16 years of age or younger, or orthostatic syncope).

Involvement of three or more of the following organ systems:

- Gastrointestinal (vomiting or diarrhea at onset of illness).
- Muscular (severe myalgia or creatine phosphokinase level $\geq 2\times$ULN).
- Mucous membrane (vaginal, oropharyngeal or conjunctival hyperemia).
- Renal (blood urea nitrogen or creatinine levels $\geq 2\times$ ULN, or $\geq$5 leukocytes per high-power field—in the absence of a urinary tract infection).
- Hepatic (total bilirubin, serum asparate aminotransferase or serum alanine aminotransferase levels $>2\times$ ULN).
- Hematologic (platelets $\leq$100,000 per cu mm).
- Central nervous system (disorientation or alterations in consciousness without focal neurological signs when fever and hypotension are absent).

Negative results on the following tests, if obtained:

- Blood, throat or cerebrospinal fluid cultures.
- Serological tests for Rocky Mountain spotted fever, leptospirosis or measles.

ULN = upper limits of normal

*Adapted from Morbidity Mortality Weekly Rep.[12,p442]

will have serum creatine phosphokinase levels more than twice the normal range; a few patients with very high levels have also had myoglobinuria.[13] In addition, hypocalcemia has also been observed, with a few patients becoming symptomatic and requiring replacement therapy.[13] The mechanism underlying this phenomenon is not known.

In its milder forms, TSS may closely resemble Kawasaki disease, an illness that generally occurs in young children and is characterized by fever, macular rash with subsequent desquamation, musculoskeletal complaints and mucosal abnormalities similar to those outlined above. Indeed, as previously noted, several adult cases initially felt to represent Kawasaki disease are now classified as examples of TSS. However, the syndromes are distinguishable on clinical and epidemiologic grounds. Hypotension and renal failure are not characteristics of Kawasaki disease, and pyuria, when present, is of urethral rather than renal origin. Analysis of urine aspirated from the bladders of these children shows no abnormalities.[18] Conversely, lymphadenopathy—a major criterion for the diagnosis of Kawasaki disease—is usually absent in TSS. Lastly, the epidemiologic features of the diseases are often helpful in separating the two. Kawasaki disease occurs almost exclusively in young children, most cases ocurring within the first four years of life.[18] While TSS may occur in children,[1] Kawasaki disease rarely, if ever, affects adults.

The other diagnosis most commonly entertained in cases of TSS is scarlet fever. In addition to the rash, many of the other associated physical findings of scarlet fever, including pharyngitis, circumoral pallor and even the classic "strawberry tongue" can be seen in TSS.[15] Again, the typical epidemiologic setting and the absence of pharyngeal group A streptococci are the most useful differential features. When headache, disorientation and thrombocytopenia dominate the clinical features, the condition can resemble meningococcemia or even Rocky Mountain spotted fever; where abdominal pain and hypotension predominate, intraabdominal infection with Gram-negative sepsis can be suggested.[13] Usually, however, the characteristic rash allows ready differentiation from these other entities.

Epidemiologic Features

The striking association of TSS with menses (Figure 1) immediately suggested that factors related to menstruation might be responsible for the recent wave of cases of this illness. Having established strict criteria for diagnosis, several groups[13,14] began examining their cases for the presence of risk factors associated with the development of TSS. Age-matched controls were selected from either acquantances of the patients[11-13] or from women attending gynecologic clinics.[14] Detailed questions were asked concerning tampon use and other hygienic practices during menses, sexual habits, contraception, previous menstrual problems, past vaginal infection and many other variables. The only major differences detected between cases and controls involved tampon use and contraceptive practices. Although 75 percent to 80 percent of control women used tampons with periods, more than 97 percent of patients were tampon users.[13,14] Among women using only one brand of tampon, one large study[12] reported a significant association between the use of Rely tampons and the development of TSS. Because of these data, this brand was withdrawn from the market in September 1980. However, it is to be emphasized that almost 30 percent of TSS cases in the same study occurred in users of tampon brands other than Rely. Among tampon users, more TSS patients than controls used tampons continuously throughout their entire period.[13] No differences were found between groups in the absorbency of the tampons used, or the volume or duration of menstrual flow; further, no relationship was noted between marital status or sexual practices and the risk of TSS development.[13,14] The only other factor that differentiated cases from controls was the finding that contraceptive use was significantly less frequent in patients than in controls. However, no one method of contraception could be shown to account for the difference, and the reasons for this finding—independently noted in two separate studies[13,14]—remain obscure at present. Speculations that contraceptive use is somehow protective against the development of TSS are premature.

Etiology and Pathogenesis

Greatly aided by the previous association of TSS in children with local *S aureus* infection,[1] evidence implicating staphylococci in the menses-related form was rapidly forthcoming. In the large CDC study,[13] *S aureus* was isolated from vaginal cultures in 97 percent of TSS cases, as compared with 10 percent of controls (cultured during a normal menstrual period). Though most of the

early isolates belonged to phage group I,[1] more extensive surveys show no unique phage group among responsible strains.[13,14] Likewise, the antibiotic susceptibilities of these staphylococci show no unusual features; most produce β-lactamase and are susceptible to nafcillin, cephalosporins and vancomycin.[6,13,15]

Many groups are now actively investigating the available isolates from TSS cases, searching for the putative toxin or other markers that might differentiate these strains from conventional *S aureus* isolates. Cohen and Falkow[19] have described two polypeptides (with molecular weights of 30,000 and 33,000, respectively) present in TSS strains that specifically react with antisera from patients convalescing from TSS. It has been suggested that such proteins could be subunits of the putative toxin of TSS, or simply antigenic markers associated with such strains. However, they were detected in only 78 percent of TSS isolates; they were also demonstrated in 25 percent of control *S aureus* strains.[19] More work is needed to define fully the relationship, if any, of these antigens to TSS.

Very recently, two groups[20,21] have reported the identification of apparently novel staphylococcal toxins from TSS isolates. Bergdoll and co-workers[20] have described a toxin, designated enterotoxin F, that was produced by 94 percent of TSS-related *S aureus;* only 5 percent of non-TSS-strains elaborated this material. This low-molecular weight, acid-stable protein was detected by virtue of its enterotoxigenic properties following intragastric injection in monkeys. Direct laboratory demonstration of a TSS-like illness induced by enterotoxin F has not yet been reported, however, and its role in the pathogenesis of this disease remains to be defined.

Schlievert and associates[21] have isolated from the growth medium of TSS strains a protein of molecular weight 22,000, which they term exotoxin C. This material was detected by virtue of its pyrogenicity in rabbits and its ability to enhance the susceptibility of inoculated animals to lethal shock caused by *Salmonella* endotoxin. All 28 TSS-related strains examined were positive for exotoxin C production; 16 percent of non-TSS strains (including several vaginal isolates from healthy women with no history of TSS) also produced this activity. No published data are available at present concerning the enterotoxigenic properties of exotoxin C, and the relationship of this protein to enterotoxin F requires clarification. Because both proteins are immunogenic,[20,21] serological as well as functional assays can, in principle, be developed to study this question. Again, as for enterotoxin F, inoculation of experimental animals with exotoxin C does not reproduce all of the clinical features of TSS.[21] Thus, its contribution to the pathogenesis of this syndrome is likewise a subject requiring further investigation.

It is not unexpected that occasional isolates from normal persons can be found to elaborate this candidate toxin or toxins in vitro; the existence of such asymptomatic carriers in no way refutes the possibility that the proposed toxin or toxins cause or contribute to the symptoms of TSS. It does, however, suggest that other bacterial or host factors are also important in its pathogenesis. Such factors could, for example, affect the ability of the organism to colonize a particular site (such as the vagina) or modulate the amount of toxin produced, absorbed from, or inactivated at such a site. The complete enumeration of all such factors may prove to be a formidable undertaking. Nonetheless, the identification of these novel toxins appears to be a promising first step in this direction.

Thus, although *S aureus* is almost certainly causally associated with TSS, clear delineation of the pathogenesis of this disease is still lacking. In view of this, one can speculate about the role tampons play in the development of TSS. Direct introduction of the organism into the vagina on the surface of the tampon has been excluded by the failure to recover *S aureus* from all brands of tampon cultured to date.[12,13] Tampon use has been shown to produce vaginal mucosal drying and even microulcerations[22]; and, though the latter usually resolve rapidly, they could be involved in allowing establishment of infection or enhancing absorption of a putative toxin. Unfortunately, such hypotheses, while attractive, remain untestable at present.

Prognosis and Treatment

The overall fatality rate from TSS has been reported to be approximately 8 percent.[9] It is likely that this figure will decline as awareness of this entity among physicians grows and milder forms of the disease are recognized.[16]

One of the striking features of TSS, at least in its menses-related form, is the propensity of patients to have recurrences. In two large series,[13,14] approximately 30 percent of women recovering from an episode of TSS experienced another epi-

sode with a subsequent period. The median time to recurrence was two months following the initial episode, though recurrences up to 41 months later have been documented.[13] Multiple recurrences were not infrequent. Usually the severity of the recurrent illness is less than that of the initial episode, but exceptions to this rule are frequent.

The proper management of a case of TSS includes, of course, careful physical examination, with particular attention to localized foci of infection (especially of skin and soft tissues). Meticulous pelvic examination in females is mandatory; tampons, if present, should be removed and vaginal cultures obtained. Cultures of blood and of any evident soft tissue foci of infections are likewise essential. The role of nasal, axillary and pharyngeal cultures[15] (in the absence of local signs of infection) has not been adequately assessed. The usual supportive measures for hypotension and renal insufficiency should be promptly undertaken where these are present.

No prospective study on antibiotic use in treating TSS has yet appeared, but retrospective examination of cases already reported[13,14] has yielded helpful insights into this question. Because of the retrospective nature of the available data, it is not possible to ascertain whether the administration of appropriate antibiotic drugs ameliorates an overt acute episode of TSS. However, it is clear that patients who received β-lactamase-resistant antibiotic drugs had significantly fewer recurrences than patients who did not. In one study,[14] only 1 of 16 women so treated experienced a recurrence within the first three months, while 9 of 13 untreated women had recurrences during this interval.

Another important reason to include antibiotic therapy at the earliest suspicion of TSS is the occasional presence of *S aureus* bacteremia.[15] While this is uncommon, bacteremic patients cannot be reliably differentiated from nonbacteremic cases on clinical grounds alone. Thus, at present, early parenteral therapy with β-lactamase-resistant antibiotic agents is strongly recommended.

Women who have had TSS are advised[13] not to return to tampon use for several months following the episode, if ever. Although this issue has not been carefully studied, it is prudent to verify by repeat culture that *S aureus* has been eradicated from the vagina before resumption of tampon use can be considered. Should such women opt to resume the use of tampons, using them intermittently (for example, for only part of the day or only part of the period) is advised. Obviously, such recommendations may be revised when more is known about the biology of TSS-related staphylococci and the natural history of their carriage in the female reproductive tract.

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Important Advances in Clinical Medicine

Epitomes of Progress — Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Dantrolene: Specific Drug Therapy for Malignant Hyperthermia

MALIGNANT HYPERTHERMIA is a fulminant hypermetabolic crisis induced by anesthetic trigger agents in genetically susceptible persons. The full-blown syndrome, with tachycardia, cardiac dysrhythmias, unstable blood pressure, fever, rigidity, hypoxemia, lactic acidosis, hyperkalemia and myoglobinemia, has a mortality of 60 percent. This syndrome has been reported in patients ranging in age from 3 months to 70 years.

Malignant hyperthermia results from a defect of membrane calcium transfer in skeletal muscle. The sarcoplasmic reticulum, in response to a triggering stimulus, releases an abnormally large amount of calcium because of abnormal "leakiness," or by its inability to reaccumulate calcium from the myoplasm back into intracellular storage sites. Excess myoplasmic calcium produces an abnormal amplification of excitation-contraction coupling. The resulting hypermetabolism and continued contraction of skeletal muscle generate heat, exhaust adenosine triphosphate stores, uncouple mitochondrial oxidative phosphorylation, and lead to further cellular and membrane derangements.

Until recently the treatment of malignant hyperthermia consisted only of supportive measures —discontinuance of anesthesia, hyperventilation with 100 percent oxygen, sodium bicarbonate for metabolic acidosis, procainamide for cardiac dysrhythmias, cooling, diuretics to prevent myoglobin from precipitating in the renal tubules, and treatment of hyperkalemia. Although it may restore blood gas and other laboratory values, supportive therapy does not alter the underlying and continuing pathological defect.

Dantrolene sodium, which acts to prevent excessive release of intracellular calcium, is one of several hydantoins synthesized by Snyder and associates in 1967 that proved to have muscle relaxant properties. Extensively investigated, dantrolene is known to act directly on skeletal muscle but has no effect on smooth and cardiac muscle. It does not affect neuromuscular transmission or electrically excitable surface cell membranes. Van Winkle showed that dantrolene is pharmacologically active within the sarcotubular system where it suppresses the release of calcium. It has proved effective in the treatment and reversal of malignant hyperthermia in both swine and humans.

Dantrolene is not a substitute for aggressive, supportive therapy—it is a specific adjunct to

established treatment. It is supplied as a lyophilized powder which is dissolved in sterile water. The initial intravenous dose for children and adults is 1 mg per kg of body weight, repeated as necessary for persistent physiological and metabolic abnormalities up to a cumulative dose of 10 mg per kg of body weight. The average cumulative intravenous dose required to abort the clinical manifestations in humans is 2.5 mg per kg of body weight. Dantrolene given orally in doses of 1 to 2 mg per kg of body weight four times a day for one to three preoperatively may be prophylactic in known malignant hyperthermia reactors. There are no reported side effects with short-term dantrolene therapy.

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Hazards of Discontinuing Drugs Before Anesthesia

RESERPINE THERAPY for hypertension used to be discontinued before elective operations. Now it is felt that there is less anesthetic risk to hypertensive patients if this medication is continued up to the time of the surgical procedure. In fact, some danger of excessive cardiovascular stress arises if, inadvertently, antihypertensive therapy is not continued. On the other hand, the *Physician's Desk Reference* suggests that drugs such as monoamine oxidase inhibitors, tricyclic antidepressants and propranolol should be discontinued preoperatively. Because discontinuation of these drugs is not without hazard (such as depression, suicide, angina or myocardial infarction), the benefits and risks must be carefully weighed.

Few patients receive monoamine oxidase inhibitors. Their interaction with indirect-acting amines is widely recognized and generally avoidable. Further, their interaction with meperidine, resulting in coma, hyperpyrexia and hypertension, although not understood, is also avoidable. However, only a minority of anesthetists view continuing a regimen of monoamine oxidase inhibitors as desirable because the adverse effects are difficult to manage.

Unlike the monoamine oxidase inhibitors, the tricyclic antidepressants do not appear to cause severe adverse effects. While they potentiate the cardiovascular effects of exogenous catecholamines, this interaction can be avoided or controlled. Tachyarrhythmia has been reported following the simultaneous administration of the neuromuscular blocking agent pancuronium (Pavulon) in combination with the inhalation anesthetic agent halothane (Fluothane) to patients receiving long-term imipramine (Imavate, Presamine or Tofranil) therapy. Because this combination of drugs usually can be avoided, tricyclic antidepressants in therapeutic doses can be safely continued perioperatively. However, it should be noted that continuation of tricyclic antidepressants restricts the choice of anesthetic agents.

An initial series of case reports on patients undergoing cardiac operations seemed to support the view that propranolol (Inderal) interacted adversely with inhalation anesthetic drugs to produce severe myocardial depression and impaired ability to respond to cardiovascular stresses such as hemorrhage. However, reports of rebound phenomena after withdrawal of propranolol soon appeared. In hypertensive patients, abrupt withdrawal of propranolol was followed by 2 to 15 days of hypersensitivity to catecholamines. However, the course of hypersensitivity is such that it permits operations to be done within 48 hours of withdrawal. In patients with severe coronary disease and angina, exacerbation of coronary insufficiency symptoms and even acute myocardial infarction and death have been reported. This "rebound" may be the result of continued physical activity or emotional stress on a heart that is no longer protected by the beta-adrenergic blocking drug. In a large controlled study of coronary artery bypass graft patients, those who continued to receive propranolol up to the day of the operation did as well as the patients in whom propranolol therapy was discontinued. It should be noted that these study patients had intensive cardiovascular monitoring and specialists in cardiac anesthesia overseeing their anesthetic care. Nevertheless, if a surgical patient does not have the signs of excessive beta receptor blockade (bradycardia), continuation of propranolol administration does not appear to present unusual difficulties.

Antihypertensive agents should be given up to the time of operation. Clonidine (Catapres), however, presents a special problem because it has a

short elimination half-time (8.5 hours) and is not available in parenteral form. In several case reports, perioperative hypertension occurred in patients after clonidine therapy was discontinued. However, in one controlled study only two out of ten patients had hypertension after clonidine was withheld preoperatively. The hypertensive response, if it occurs, can be managed with hydralazine or sodium nitroprusside. One group of investigators has recommended preoperative withdrawal of clonidine and propranolol, when they are given together, and substitution of hydralazine.

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Pharmacological Prophylaxis Against Acid Aspiration

THE RISK of pulmonary aspiration of gastric contents associated with general anesthesia is of major concern. The inhalation of gastric juice with a pH of less than 2.5 and in a volume exceeding 0.3 ml per kg of body weight results in a severe and intense respiratory distress syndrome. Mancuvers to protect and isolate the airway have been developed; however, accidental aspiration from either reflux or active vomiting still ocurs. Therefore, pharmacological agents that will raise intragastric pH, hasten gastric emptying, elevate lower esophageal sphincter tone or decrease the volume of gastric secretion are being investigated.

Oral administration of antacid suspensions effectively raises intragastric pH and has become routine, if not obligatory, in patients at high risk for aspiration, such as pregnant women in labor. However, recent data suggest that aspiration of the antacid suspensions leads to a pulmonary syndrome as severe as acid aspiration itself, with more persistent pathological changes. Nevertheless, while clinical experience with antacid aspiration is limited and conflicting, the use of these agents in appropriate situations is still recommended.

Cimetidine, a gastric histamine H_2 receptor antagonist, substantially elevates gastric pH in many situations when used as a premedicant. It has gained widespread usage, but its efficacy and safety in pregnant women has not yet been confirmed. Further, it does not reliably decrease the volume of gastric contents in preoperative patients and it prolongs the action of some benzodiazepines.

Metoclopramide, a chlorbenzamide derivative will be available soon in the United States. It is an antiemetic agent that accelerates gastric emptying by sensitizing gastric smooth muscle to the action of acetylcholine, as well as having a direct autonomic effect. It has been shown to be effective in pregnant women in labor.

Domperidone, an investigational drug, is a benzimadazole antiemetic that elevates lower esophageal sphincter tone. This agent may have a useful application after further clinical trials are completed.

Reduction in the volume of gastric secretions has been partially successful with anticholinergic agents such as glycopyrrolate. Glypyrrolate also raises gastric pH in some patients. However, both glycopyrrolate and atropine decrease lower esophageal sphincter tone, thereby increasing the risk of reflux. This effect is antagonized by both domperidone and metoclopramide.

Meticulous attention to securing the airway mechanically is the key to the prevention of aspiration pneumonia. However, the use of one or more of the above pharmacological agents may provide extra protection to patients at high risk for aspiration.

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High Frequency Ventilation

TRADITIONAL MECHANICAL VENTILATION involves cuffed endotracheal tubes and large tidal volumes (12 to 15 ml per kg of body weight) given at slow rates (8 to 15 breaths per minute), with or without positive end-expiratory pressure (PEEP). It has been extremely successful in optimizing oxygenation in patients with serious lung disease, but it has serious drawbacks due to the high air-

way pressures generated, particularly when the lungs are noncompliant. This may lead to various forms of barotrauma (such as pneumothorax or subcutaneous and mediastinal emphysema) as well as cardiovascular effects, including a reduction in cardiac output and blood pressure or an increase in venous pressure leading to raised intracranial pressures, hepatic engorgement or increased renal vascular resistance. Further, it is often difficult to synchronize a patient's breathing with a ventilator without resorting to the use of sedatives, narcotics or muscle relaxants, all of which have certain risks and which obscure useful clinical information, particularly in the presence of neurological disease. Thus, alternative methods of ventilation, including high frequency positive pressure ventilation (HFPPV), have been studied.

There are many devices used for HFPPV (at present each investigator must build his own); however, all are designed to deliver small tidal volumes (less than 3 ml per kg of body weight) at rates which vary from 60 to 2,400 breaths per minute (1 to 40 Hz). At lower rates (less than 5 Hz), most systems employ an "open" circuit with a pulsatile jet of gas injected into the airway by way of an open endotracheal tube or transtracheally. Conventional closed, valved circuits can be used if the ventilator is equipped with small diameter, noncompliant tubing, having minimal compression volumes, and if it has a high-rate capability. High frequency oscillation (HFO) machines may either use a similar technology or employ a simple to-and-fro piston with a single hose circuit by which fresh gas is delivered near the patient (similar to a Mapleson D). With this method, carbon dioxide absorption is unnecessary.

The classic view of respiratory physiology states that very low volumes lead to atelectasis and accumulation of carbon dioxide (because only the "dead space" is ventilated). However, this has been disproved repeatedly by studies using the high frequency ventilation systems. These systems are capable of providing long-term support with normal gas exchange and without evidence of atelectasis, in spite of peak airway pressures of less than 5 to 8 cm of water. However, in the presence of severe lung disease PEEP may still be needed. Gas exchange does not depend on bulk gas movement (hence, anatomical dead space becomes less important); instead it acts as "facilitated diffusion" in which agitation of the intrathoracic gas constantly mixes fresh and alveolar gases.

HFPPV and HFO methods have many advantages. Lower airway pressures may minimize the risks of barotrauma and clearly reduce air leaks from bronchopleural fistulas, thus promoting healing. They may also prove useful in supporting patients following pneumonectomy in whom there is a risk of bronchial stump disruption. These lower pressures may improve cardiac output although this can be offset if PEEP is required. Several groups claim that clearance of secretions is enhanced, possibly because the constant vibration is percussive. Another benefit is the reflex suppression of spontaneous respiratory drive (without hyperventilation), perhaps due to an alteration in stretch receptor stimulation, which can minimize the need for sedatives and ease patient acceptance of the ventilator. This may not be true in the presence of very severe lung disease although some devices also allow simultaneous, spontaneous breathing during HFPPV. HFPPV may also reduce ventilatory-synchronous movement of various organs (such as the brain, lung and diaphragm) making the surgical procedure easier.

High frequency techniques represent a major new approach to mechanical ventilation, although commercial equipment is not yet available. However, it will be several years before all of the benefits and disadvantages are known and the physiology completely understood.

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Isoflurane: A New Inhalation Anesthetic

ISOFLURANE (FORANE) was first synthesized in 1965 by Ross C. Terrell of Ohio Medical Products, following the development of its isomer, enflurane (Ethrane), which has been in clinical use since 1973. Isoflurane has undergone extensive studies in animals and in humans and has been approved by the Food and Drug Administration for use in the United States. It is also used in Canada.

Isoflurane, a fluorinated ether, is a nonflammable, clear, colorless, stable liquid that contains no additives or chemical stabilizers. Induction of

isoflurane is fairly rapid at 1 percent to 4 percent inspired concentration. This agent has mild pungency, which may limit the rate of induction in some patients, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. The depth of anesthesia can be easily altered by controlling the inspired anesthetic concentration. Recovery from anesthesia is usually smooth and rapid, and no significant incidence of nausea or vomiting has been observed.

Anesthesia is maintained with 0.8 percent to 2 percent inspired concentration of isoflurane. The agent is a potent respiratory depressant and, hence, respiratory status needs to be closely monitored and supported when necessary. This depression is partially reversed by surgical stimulation. Systemic blood pressure decreases with induction of anesthesia as a result of a decline in the peripheral vascular resistance, an effect similar to that of enflurane and halothane. Blood pressure returns toward normal values on commencement of the surgical stimulation. With regard to its cardiac effects, isoflurane is superior to both enflurane and halothane because it does not decrease myocardial function or cardiac output during moderate depth of anesthesia. Isoflurane does not appear to sensitize the myocardium to catecholamines (epinephrine). There is a modest increase in heart rate under isoflurane, irrespective of the anesthetic concentration. This effect is in contrast to that of enflurane, which produces a dose-related increase in heart rate and that of halothane, which causes no increase in heart rate. Isoflurane is free from the central nervous system excitatory properties of its isomer, enflurane. It produces excellent muscle relaxation as does enflurane, is roughly two to three times more effective than halothane, and greatly potentiates all muscle relaxants.

Of all the halogenated anesthetic agents, isoflurane is the least metabolized in humans or animals. This relative stability strongly indicates that the agent should have no potential to produce organ toxicity. Studies carried out in humans and animals also suggest little or no effect on the liver or kidney, and there is no evidence to indicate the carcinogenicity of isoflurane.

Isoflurane claims superiority over several other inhalation anesthetics for its effect on the cardiovascular system, the central nervous system, the neuromuscular system, anesthetic metabolism and organ toxicity. Its drawbacks include a pungent smell, considerable respiratory depression, tachycardia and hypotension. The full potency of this anesthetic agent will not be known until it is administered to several thousand patients for various surgical procedures. Isoflurane is not perfect, but it comes one step closer to being an ideal inhalation anesthetic agent.

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The Role of Ketamine in Obstetric Anesthesia

DESPITE INITIAL FAVORABLE EVALUATION of therapy with low doses of ketamine (0.5 mg per kg of body weight) in obstetric patients, the drug has not been widely used during delivery for two reasons: First, several subsequent investigators showed significant neonatal depression with higher doses (2 to 5 mg per kg of body weight) of the drug. Although later evidence showed that low doses (0.2 to 0.4 mg per kg of body weight) did not have a substantial depressant effect on newborn infants, the decline in ketamine's use caused by the earlier results persisted. Second, there is a growing, and laudable, trend away from the use of general anesthesia in obstetrics. Consequently, there is no indication for the large doses of ketamine (1 to 2 mg per kg of body weight) used to induce general anesthesia.

Ketamine is becoming more popular as an intravenously administered *analgesic* for the second and third stages of labor. When very low doses of the drug are given women for whom regional or inhalational methods of analgesia are unsuitable, consciousness and patient cooperation are maintained and relief of pain is excellent. Because the mother retains her protective airway reflexes, endotracheal intubation is not required, and high flows of oxygen can be administered by face mask. Some of the other problems often associated with larger doses of ketamine are not seen with the low-dose technique. For example, hypertension and tachycardia occur only rarely, and bad dreams or hallucinations are similarly infrequent.

Two intravenous doses of 5 to 10 mg of

ketamine usually will provide sufficient analgesia for a normal, uncomplicated vaginal delivery. Administration of bilateral pudendal nerve blocks or perineal local infiltration will further enhance the effects of the analgesia and will obviate the need for repeated injections during the second and third stages of labor.

Doses of ketamine larger than 1 mg per kg of body weight can have negative effects on the newborn and should, therefore, be avoided in obstetric care. However, very low doses (0.1 to 0.2 mg per kg of body weight) given intravenously provide effective analgesia for the second and third stages of labor without causing significant complications in the mother or infant.

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Issues in Obstetric Anesthesia

THREE NOTEWORTHY ISSUES in the use of anesthesia in obstetric patients are (1) continuous-infusion epidural analgesic agents, (2) the safety of 2-chloroprocaine and (3) the neurobehavioral consequences of epidural anesthesia in newborns.

Continuous-infusion epidural analgesia has recently gained wider acceptance as an efficient tool for regional anesthesia because it allows sophisticated anesthesia to be given safely and efficiently to a larger number of women who are in labor. Bupivacaine, 0.25 percent, is infused in a volume of 6 to 12 ml per hour by constant infusion pump after safe placement of an epidural catheter and response to the drug has been confirmed. Care of the patient includes half-hourly blood pressure measurement and leg lift test to avoid motor blockade. The result is a steady level of analgesia with fewer peaks and valleys of pain, less sympathetic block, less motor loss and lower peak blood levels of bupivacaine than are often seen with intermittent injection.

There have been recent case reports of neural damage after subarachnoid injection of 2-chloroprocaine, although results of numerous studies in the United States have shown that 2-chloroprocaine is no more toxic than other local anesthetic agents. Large-scale statistical comparisons of epidural anesthetic administration in humans have shown an incidence of neurological injury of 1 in 11,000.

Laboratory animal preparations of nerves exposed to local anesthetic solutions have been compared. Prolonged exposure of mammalian nerves to chloroprocaine produced no evidence of nerve injury. Most physicians who use this agent and the Food and Drug Administration as of December, 1980, agree that 2-chloroprocaine is safe for use in obstetric patients. The advantages of rapid onset, short duration, short plasma half-life and minimal placental transfer justify its continued use as an alternative drug in regional anesthesia.

Results of controversial studies have indicated that obstetric anesthesia may cause brain damage in some newborn infants. The validity of these assertions has been recently challenged by neonatal behavioral scoring techniques, including Brazleton, Scanlon and the newer ABS (Amiel-Tison, Barrier and Shnider). Hodgkinson, Scanlon and others have found no measurable differences in neonatal scores between babies delivered with or without epidural bupivacaine. This conclusion applies equally to babies born by vaginal delivery and by cesarean section. A good result depends on a high standard of anesthetic care, parsimonious anesthetic dosages and promotion of maternal cardiovascular and respiratory well-being.

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Aminophylline, Arrhythmias and Anesthesia

AMINOPHYLLINE (theophylline ethylenediamine) is the most widely used bronchodilator in the United States. Frequently, it is given preoperatively to asthmatic patients before the anesthetic is administered as well as intraoperatively for the treatment of bronchospasm. Halothane is considered the anesthetic agent of choice for asthmatic patients because of its bronchodilating effect.

There have been no reports of cardiac arrhythmias occurring in patients following intraoperative

administration of aminophylline. Investigation of the arrhythmogenic effects of aminophylline given during halothane anesthesia in animals has shown that doses that produce blood levels corresponding to the therapeutic, nonarrhythmogenic range in conscious humans (10 to 20 mg per liter) are likewise not arrhythmogenic in animals. However, studies of the effect of higher, toxic doses of aminophylline (producing levels in the blood above 20 mg per liter) administered to animals during halothane anesthesia have shown that these high levels (which repeatedly have been shown to cause severe cardiac arrhythmias in conscious humans) are, in fact, arrhythmogenic in anesthetized animals.

In recent years, there have been reports of ventricular arrhythmias occurring in patients during halothane anesthesia following preoperative administration of aminophylline. Studies have been done in animals of the arrhythmogenic effects of aminophylline administered before anesthesia induction. Results have shown that even at theophylline levels in the blood that are considered safe in humans, ventricular arrhythmias frequently occur in the animals following induction of halothane anesthesia. In contrast, induction of enflurane anesthesia in animals appears safe even after toxic doses of aminophylline have been given.

On the basis of available information, the following guidelines are suggested for perioperative administration of aminophylline in humans. First, aminophylline given intravenously during halothane anesthesia in doses that produce accepted therapeutic levels (10 to 20 mg per liter) in the blood is unlikely to cause cardiac arrhythmias. A safe dose that is likely to produce such a level is 5 mg per kg of body weight for a patient who has not received aminophylline in the previous 24 hours (1 mg of aminophylline per kg of body weight will produce a 2 mg per kg of body weight rise in blood level). The drug should be diluted in 50 ml of sterile fluid and administered only by way of a peripheral intravenous route over five minutes. *Aminophylline given by way of a central venous line or pulmonary artery catheter often results in sudden death.*

Second, if aminophylline has been administered preoperatively, induction of halothane anesthesia may produce severe ventricular arrhythmias, even with circulating theophylline levels normally considered therapeutic and safe in conscious patients. Enflurane anesthesia used after preoperative administration of aminophylline, however, appears safe and unlikely to precipitate cardiac arrhythmias.

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Butorphanol and Nalbuphine: Two New Potent Analgesic Agents

TWO NEW ANALGESIC DRUGS have been released recently for the treatment of moderate to severe pain. Like pentazocine, these two drugs have mixed agonist-antagonist properties, which, it is hoped, will produce the *perfect balance* of analgesia without psychological or physiological effects.

Butorphanol tartrate, chemically related to levorphanol tartrate, is available in a 1 to 2 mg per ml solution; on a milligram basis, it has 3½ to 7 times the potency of morphine. Following intramuscular administration, it is rapidly absorbed, achieving a peak plasma level in 30 to 60 minutes, with a half-life of three hours.

In equianalgesic doses, respiration is depressed similarly with morphine or butorphanol. Interestingly, an increase in dose of butorphanol reportedly increases the duration, but not the degree, of respiratory depression. The hemodynamic effects of butorphanol resemble those of pentazocine, causing an increase in pulmonary artery and right atrial pressure with a decrease in cardiac output. However, the unpleasant psychotomimetic side effects reported with pentazocine occur only rarely with butorphanol. Euphoria does not result from butorphanol administration, and its addiction potential is judged to be low.

Nalbuphine, chemically related to oxymorphone and naloxone, is available in a 10 mg per ml solution; on a milligram basis it is variably reported to be equal to, or a half to a third as potent as, morphine. Following intramuscular administration it achieves effect in 15 minutes and maintains activity for three to six hours. The respiratory effects of nalbuphine resemble mor-

phine but, like butorphanol, there is a "ceiling" beyond which a further increase in dose does not increase the degree of depression. Cardiovascular effects differ from those of butorphanol, however, in that nalbuphine more nearly resembles morphine, having no significant impact in most patients on cardiac output or arterial, right atrial or pulmonary artery pressure. Nalbuphine has been given with favorable results to patients following myocardial infarction. The abuse potential of nalbuphine is judged low but is probably slightly greater than that of butorphanol.

The actions of both drugs are reversed by naloxone and they can precipitate withdrawal reactions in patients receiving long-term opiate therapy. At present they are not classified under the Controlled Substances Act. However, caution is advised—initially, meperidine and pentazocine were also thought to be nonaddicting. Butorphanol and nalbuphine should be treated like any potent parenteral mood-altering drug until time proves this unnecessary.

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Oxygen Monitoring

IN CLINICAL PRACTICE oxygen monitoring includes the sensing of gaseous oxygen in inspired and expired air, dissolved oxygen in arterial and venous blood, oxygen saturation in blood and tissue and whole body oxygen uptake. Rapidly progressing technology is providing monitoring instruments that are easier to use and less invasive.

Gaseous oxygen is monitored best by the polarographic technique. Four major manufacturers (Critikon, Instrumentation Laboratory, Teledyne and Beckman) produce such monitors, which cost between $300 and $600. The sensors, which are mounted directly in a patient's breathing circuit, have a life time of 3 to 12 months. These monitors, with direct readout and alarms, are considered standard equipment in many hospitals. More sophisticated monitors, including multiplexed mass spectrometers, paramagnetic sensors and heated fuel cells, are more accurate; however, because of their expense and size are used mainly as research tools.

Dissolved oxygen in arterial and venous blood is usually measured offline by bench instruments. New automated blood gas analyzers (Radiometer, Corning, Instrumentation Laboratory and Technicon) use microprocessors to perform automatic calibration, temperature compensation and simple calculations. Automated machines are two to three times more expensive than manual machines but they often replace a laboratory technician. A continuous monitor of dissolved oxygen is available from Critikon, but it has been designed for extracorporeal monitoring. Transcutaneous oxygen ($TcPo_2$) monitors, using heated Clark electrodes, provide information on arterial oxygen pressure (Pao_2) without the need for arterial puncture (Biochem, Radiometer, Litton, Novametrix and Roche). It must be realized that in adults, $TcPo_2$ is a measure of oxygen delivery and not Pao_2.

The oxygen saturation of arterial and venous blood can be measured offline with bench infrared (IR) instruments (Radiometer, Instrumentation Laboratory) or in vivo, using fiberoptic catheters (Physio-Control). The fiberoptic arterial and Swan-Ganz catheters are used to measure oxygen saturation by way of IR reflectance oximetry at the tip of a catheter. This method is invasive, the catheters are expensive ($50 to $70) and clot formation on the catheter tip can be a problem. Oxygen saturation can be monitored noninvasively using IR absorption through either the ear lobe or finger. (Hewlett-Packard and Corning) Because multiple wavelengths are needed to compensate for differences in skin pigmentation and movement artifacts, these instruments are cumbersome and expensive. Oxygen content, sometimes a more meaningful determination, is measured only offline (Cavitron).

The monitoring of oxygen at the tissue level is useful in detecting the shutdown of peripheral blood flow as an early indication of shock. Bare platinum wires have been used for monitoring in research studies but not for patient monitoring because of noise considerations. Solid state sensors and miniature polarographic sensors are being investigated.

Whole body oxygen consumption (Vo_2) is an indirect measure of a patient's metabolic requirements and may be used to monitor the incidence of shock. During administration of anesthesia, the Vo_2 may be related to depth of anesthesia. To monitor Vo_2 in the intensive care unit (ICU), mass spectrometer systems are multiplexed between several beds. Thus patients can share the

expense of these sophisticated systems (Perkin-Elmer, Centronics and Cemetron). In the future V_{O_2} monitoring will be an integral part of the ICU ventilator. During anesthesia, V_{O_2} has been monitored and studied using closed-circuit breathing circuits, in which the inflow rate of fresh oxygen is a measure of V_{O_2}.

Oxygen monitoring technology is rapidly progressing. Soon gaseous monitoring will become standard equipment on each breathing circuit. Additional improvements to and experience with transcutaneous techniques should make it possible to monitor Pa_{O_2} and oxygen saturation continuously and noninvasively. Further, continuous monitoring of gas exchange, V_{O_2} and V_{CO_2} will become a standard procedure for patients needing ventilation.

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Barbiturates and Cerebral Ischemia

BARBITURATES CAN REDUCE cerebral metabolic rate, cerebral blood flow and cerebral blood volume by as much as 50 percent, and the administration of these drugs is a well-known method for controlling or reducing intracranial pressure (ICP). Recently, they have been advocated for the treatment of various forms of cerebral ischemic, hypoxic or anoxic insults (such as transient cardiac arrest, stroke, near drowning or asphyxia) or for the intraoperative "protection" (pretreatment) of patients at risk for such insults as occlusion of a carotid or cerebral artery, profound hypotension or circulatory arrest. The rationale for their use is the theory that tissue damage can be minimized if metabolic demand is reduced at a time of decreased oxygen and nutrient delivery, although other ideas have been presented (such as free radical scavenging or redistribution of regional cerebral blood flow). Unfortunately, there are discrepancies between this theory, experimental data and clinical observations.

There is laboratory evidence that pretreatment with barbiturates protects the brain in situations of *incomplete* ischemia or hypoxia (not anoxia). Barbiturate anesthesia prolongs survival in hypoxic mice, slows the metabolic deterioration of the brain (such as lactate accumulation and adenosine triphosphate depletion) during profound hypotension (blood pressure less than 40 mm of mercury) and can also reduce the size of experimental strokes produced by middle cerebral artery occlusion, at least if given before cell death has occurred (within one to two hours after occlusion). However, large doses (sufficient to produce an isoelectric EEG) are needed. Unfortunately, there are no data on humans that confirm these observations, and the clinical relevance is limited.

There is no evidence that treatment begun after reperfusion or reoxygenation is useful, except to control ICP, and there are few opportunities to "treat" patients before severe hypoxia. Similarly, the cardiovascular depressant effects make it unwise to administer large doses of barbiturates during accidental hypotension. Elective protection before planned profound hypotension (not *routine* hypotensive anesthesia) would be better achieved by hypothermia, which also can be more readily reversed, particularly if cardiopulmonary bypass is used. Barbiturates might be considered in conjunction with "emergency"-induced hypotension when there is a risk of brain damage, such as after intraoperative rupture of a cerebral aneurysm. However, the only anecdotal evidence concerns cases of elective or emergency cerebrovascular occlusion, at least when the tissue is eventually revascularized. Unfortunately, there are no post-stroke studies, principally because of the obvious concern with cardiovascular and respiratory depression in elderly patients. Therefore, with the exception of the hypothetical uses just mentioned, it is difficult to support the use of these drugs. Barbiturates should not be used routinely as an adjunct to carotid endarterectomy, because most patients tolerate transient cross-clamping without problems. If clamping produces ischemia (EEG depression) that cannot be reversed by raising blood pressure or by shunt placement, such use might be considered.

The most controversial use of these drugs is after resuscitation from a cardiac arrest. Recent debate was prompted by a single primate study, which has been questioned on both procedural and theoretical grounds. Other studies have not confirmed the efficacy of barbiturates given before or after a period of circulatory arrest, in contrast to the proven usefulness of hypothermia before

the time of the arrest. More importantly, uncontrolled trials have shown no benefit, and results from a preliminary nonrandomized study of thiopental given after resuscitation have shown no improvements in mortality or neurological morbidity. Therefore, there is *no* evidence supporting the "blanket" administration of these drugs to patients following cardiac arrest, although they may prove useful in treating postanoxic seizures in some persons. There is, however, some circumstantial evidence supporting an aggressive approach to these patients, and careful respiratory and cardiovascular support may be of value.

In spite of intriguing laboratory evidence, the clinical role of barbiturates in brain protection remains unproved, except for control of ICP (which probably has nothing to do with "protection" per se). In highly select intraoperative situations, their use can be justified—if used with great caution. However, there is no role for these drugs in treating patients following cardiac arrest.

MICHAEL M. TODD, MD

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EDITORIALS

On the Value of Case Reports

IT IS A PLEASURE to discuss the splendidly studied and carefully cared-for patient that Drs. Olerud, Robertson, Hossack, Nelp, Cdl:nd, Bowman and —an unlikely et al—Clement Finch have described for you elsewhere in this issue in the Pathophysiological Conference. Dr. Finch had called me about this patient and then sent details and photographs of the vascular lesions and some of the physiological studies. I was amazed, but not surprised because I could not with assurance explain the nature of the vascular changes in the skin. Below is the response I sent on the eve of New Year's Eve. I did not have all the sophisticated studies that have at least told us a lot about what was not going on.

30 December 1980

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DEAR CLEM:

I was really fascinated by your discussion and I'm even more fascinated by the case report, the descriptions and the photographs. Even if I had seen your patient and could palpate as well as directly inspect the lesions, I couldn't possibly know more than you have sent me in the enchanting and entrancing description of your patient. Any individual lesion, I believe, would pass as an arterial spider. Some are wildly growing angiomas and I have seen them—one that I could barely cover with my hand that pulsated like an AV aneurysm, where the femoral artery and vein had been smashed up and joined forces. Since we really don't know what causes arterial spiders, although we know a lot about the circumstances under which they arise, I should be happy to say that this is more in keeping with the variation on spiders rather than a new mutation producing hereditary hemorrhagic telangiectasia. On the other hand, I've grown slowly unwise enough to believe that so many of the things that we bracket and give a name to, stop our thinking. We say this is thus-and-so rather than here is the state, process, goings on that we should be interested in and try to find the significance of. Thus, you will perhaps feel better that I cannot bracket the lesions you tell me of, but I am convinced that they are, for the most part, structures more nearly akin to arterial spiders than to the telangiectatic ones seen in Osler's disease. As I understand the derivation of the words, an angioma means growth and overgrowth and telangiectasis means a dilation of vessels at a distance. I would urge those of you who have spent much time and attention on this citizen to see if you can follow him throughout what I hope is a course of improvement and find out, perhaps by further studies of individual lesions over the years, what actually happens to him; perhaps at long last do an analysis of all the tissues.

During the past 35 years since I wound up my medical career in the army by publishing one of the very few monographs that came out of work in internal medicine in World War II (it was on vascular spiders), I've had perhaps nearly a hundred people detailing bits and pieces of a person's problems and asking me to give them an answer. This is the most elegantly studied patient I have been asked to make comment upon and, therefore, it seems appropriate that I cannot tell you in any simple terms just what's going on. One of the important things to realize about such people is that (and this is true particularly of Osler's disease, hereditary hemorrhagic telangiectasia) when they die and are examined after death, all those arterial lesions so spectacular in the skin disappear. Thus, we have no understanding at all of what goes on within the inner reaches of the body unless, as is true in the case of the lung, we can find that there must be a great many open shunts fetching blood past the eagerly panting alveoli without letting it unload carbon dioxide and take on oxygen.

I've been fortunate over the years to have gotten in touch with people through things they have written or things I have written. Thus, I am grateful to review but not solve a problem. Review it I can. Solve it, we'll have to wait for wiser people and so in the season between Christmas and New Year's, when I dictate this letter, I

send you and your group my happy greetings with pride that you have come to me even though I can do little more than the juggler at Notre Dame.

Yr serv't,
Bill
WILLIAM B. BEAN, MD

Discussion

A festive mood cannot disguise flaws in our understanding. Nearly five decades ago I naively asked certain high priests of American internal medicine at Johns Hopkins and at Harvard what those red spots were that developed in people with bad liver disease. Many very good doctors had never heard of them. Others said vaguely that they came along with jaundice. Some seemed to think my question was a silly one, but I continued to ask. Then at Cincinnati, with the late Morton Hamburger and Donald Forster, we began a study that provided me with records of some 250 persons with vascular spiders. It turned out that vascular changes were rare in obstructive jaundice. Here was a helpful clinical rule of thumb to separate medical from surgical liver disease. Dermatologists began to call me in to see lesions in patients. When I observed vascular spiders in the pregnant wife of a medical resident, he thought of acute yellow atrophy and so did I. But she was perfectly well and not jaundiced. I advised careful observation, but expected a satisfactory outcome. She was never sick during pregnancy. The lesions increased in size as her pregnancy progressed and a few new ones appeared. Then suddenly at the time of delivery the lesions diminished and rapidly disappeared. She and the baby were quite normal and the baby had no birth marks or visible vascular lesions.

After I had collected the records of the patients I began to read medical writings—going through the complete files of the *New England Journal of Medicine, JAMA, The Lancet, The British Medical Journal* and the *American Journal of the Medical Sciences,* as well as journals of dermatology and syphilology in English, French and a few in German. In the meantime I had come across the paper by Walsh and Becker, who had collected some examples of vascular spiders and palmar erythema. This caused me to go back to my notes, and I found that I had drawn several examples of palms of patients where I was looking for spiders. These patients had the classic "liver palms" or palmar erythema, but I had not paid any attention to my observation. I was, indeed, fact blind. In addition, I had collected a considerable number of examples of both palmar erythema and vascular spiders in pregnant women, and I continued these observations until I went into the army in 1942.

During four years in the army I had an opportunity to collate the clinical experience and relate it to what I had been able to glean from wide reading in internal medicine and dermatology. I was able to write and rewrite a monograph on vascular spiders that appeared in *Medicine* in September 1945, shortly after the end of World War II. I thought that what had been a stimulating and most interesting hobby would have small appeal. But as it turned out hepatitis was the great epidemic infection of World War II and there was a remarkable worldwide interest in liver disease of all kinds and various clinical signs. So what I had thought might be a small pebble dropping into a big pond turned out to create sizable ripples.

The patient under consideration here does not fit snugly into any diagnostic pigeonhole I am aware of. He exhibits the plastic changing ways of nature in health and disease. It gives me some repose of spirit to realize that the computer will never solve the problems of such folk because machines are not likely to encompass the whole of nature. And while there is a somewhat scornful attitude concerning case reports and medical experiences that are anecdotal, they are the original source of whatever medical learning we have and, indeed, can be the beginning of medical wisdom. The expression "exception proves the rule" is a bad translation of what means "the exception probes or tests the rule," and so by slow degrees we learn.

In the organization of information necessary for classification and bracketing, many conditions have to be forced into the so-called textbook picture. This, to begin with, is merely the average or composite of experience that physicians have had with patients—with a great variety of persons who have been impinged upon by the same stimuli or forces. One rarely sees a patient in whom all manifestations of a disease are right in the middle of the composite picture. On the other hand, we need to take the shortcuts that enable us to discuss and think about particular diseases as well as particular patients. But we must be steadily vigilant lest we fall into the error of believing diseases are entities. A disease is a process; the reaction of a unique person to some single force, or multiple forces, of stress or injury, existing and changing at a particular period

in time. When rare and exceptional patients appear we must study them carefully and report them with the notion that someone else may have had a similar experience. And when enough information accumulates, the pattern may be generalized, an idea of the pathogenesis and cause worked out and empirical treatment superseded by prevention.

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Yet Another Assumption About Health Care Costs

THERE IS GOOD REASON to be wary of the assumptions upon which the federal government bases many of its initiatives and interventions to control the costs of health care. The most recent assumes that, given the opportunity, consumers will be motivated to choose their health care plan or the health care they use on the basis of cost. The current rhetoric from the federal government seems to accept this as a given, even though what experience there is to date suggests that it may not necessarily be true. People do not always buy the least expensive vitamins, or even need vitamins at all, yet through personal choice many dollars are spent on vitamins and expensive ones at that. And experience with the Federal Employee Health Benefit Program and in markets with high health maintenance organization (HMO) concentration indicates that, in the past at least, consumers have not based their choice of plans primarily on economic factors.[1]

One is reminded of other assumptions by government that either have turned out to be wrong or seem likely to prove so. The widely publicized assumption that physicians' fees were the principal cause of rising health care costs certainly proved false, and the government's remedy certainly did not work. There are others that right now are in the process of not working very well or at all. For example, it has been assumed by the government that Professional Standards Review Organizations (PSRO's) would lower health care costs, that consumer dominated health systems agencies (HSA's) would reduce costs, that greater use of physician's assistants and other so-called midlevel practitioners would reduce costs, and that more competition among more doctors would reduce fees and therefore lower costs. So far none of these initiatives or interventions have fulfilled the expectations of government and many have actually added to the total cost of health care.

This most recent assumption is now to be tested —probably also on a massive scale. If consumers should happen to choose what they considered the best health plan rather than the cheapest, the result could easily be that this assumption too will not fulfill the government's expectations and may even add to the total cost of health care. It sometimes seems almost as if some of the important health policy makers live in a fantasy world where things are as they wish they were, rather than in a real world where they are as they are. This could also explain why many things have come to be as they now are.

—MSMW

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Tests of Pancreatic Function

MANY CLINICIANS are wary of pancreatic secretory tests. These tests do not seem to be sensitive or specific enough to warrant the time, patient discomfort, special expertise or expense that they require. The multitude of proposed tests, skeptics say, supports their contention that a good pancreatic function test has yet to be invented.

Elsewhere in this issue, Goff reviews the various available tests. By their very nature, most are not likely to be precise. Tests measuring hydrolysis and absorption of orally administered compounds (triglycerides labeled with carbon 14, PABA-tyrosyl esters or radioactively labeled vitamin B_{12}) depend on many factors in addition to hydrolysis of the ingested substrate by pancreatic enzymes in the gut lumen. Gastric emptying, intestinal transit, postabsorptive metabolism and excretion of the test substance (in urine or breath) are all variables that may affect such tests of pancreatic function. Likewise, colonic transit and bacterial degradation are two extrapancreatic factors that may affect fecal concentrations of pancreatic enzymes. Duodenal intubation to measure the delivery of pancreatic enzymes close to their source eliminates many of these extrapancreatic variables; however, considerable imprecision is unavoidable. Results may be affected by dilution of pancreatic secretions with meal contents (in the Lundh test) or intestinal juices, autodegrada-

tion of secreted enzymes, or partial neutralization or absorption of secreted bicarbonate.

Furthermore, pancreatic responses to defined stimuli (for example, intravenous administration of secretin) vary. Standard deviations in groups of normal subjects range from 25 percent to 60 percent of the means. With the secretin test, such wide variation is encountered whether or not the investigator uses a dye dilution indicator (to correct for inadequate aspiration of secreted volume, dilution of secreted bicarbonate, or both); and the variability is observed even when secreted juice is collected directly from the endoscopically cannulated pancreatic duct.[1,2] Because cannulation of the duct eliminates all extrapancreatic variables, one can only conclude from such observations that a wide range of responses is inherent to the normal pancreas itself.

What this variability means to diagnosticians is that all tests of pancreatic function are likely to be insensitive. They will reliably detect only the most severe impairments. Thus, it is not cost effective for a clinician to rely on a secretin or Lundh test to tell him whether the abdominal pain the patient is having originates in the pancreas, either from chronic or recurrent pancreatitis, or from pancreatic cancer. The literature is filled with inappropriately optimistic reports on the reliability of these two tests. Although the data do show that groups of patients with chronic pancreatitis or pancreatic cancer have mean responses significantly below the normal mean response, wide variation makes assessment of the result in an individual patient very difficult. For example, a third to a half of the patients with chronic pancreatitis or pancreatic cancer in such reports fall within two standard deviations of the normal mean response[2-4]; that is, they could not be distinguished from normal. While a positive result would be specific for pancreatic disease (but would not distinguish cancer from chronic pancreatitis), a third to a half of patients with disease would go undetected; thus, the diagnostic efficiency of the tests is only fair. Alternative initial procedures (such as ultrasonic examination or computerized tomography) may be nearly as specific and more sensitive for pancreatic cancer,[5-7] but less time-consuming, uncomfortable and expensive. The diagnosis of chronic pancreatitis is usually obvious. Where it is not, endoscopic pancreatography (ERCP) is about as sensitive and specific as pancreatic function tests.[8-10]

In contrast to the clinical problem of localizing abdominal pain to the pancreas, pancreatic function tests are very sensitive and specific in diagnosing exocrine pancreatic insufficiency. Pancreatogenous malabsorption represents advanced or end-stage disease of such severity as to be reliably detected by pancreatic function tests. More than 85 percent of normal pancreatic secretion has to be lost in patients with pancreatic disease before malabsorption of food begins.[11] With this degree of impairment, the secretin and Lundh tests rarely fail to detect disease,[4] and even the indirect tests (such as oral tests or fecal enzymes) are usually positive. Quite simply, so much pancreatic function has been lost that the deficiency will not be obscured by normal variation or by imprecisions in the tests themselves. The problem in this situation is not whether the tests can reliably diagnose pancreatic insufficiency but whether these frequently laborious procedures sufficiently increase the certainty of a clinically obvious diagnosis to make them worth their trouble.

In adults, 75 percent of cases of pancreatic insufficiency seen at University of California, Los Angeles (UCLA) hospitals are the outcome of end-stage, long-standing, alcohol-associated, pancreatitis. Nearly all of these patients present with weight loss and foul diarrhea, a long history of recurrent episodes of pancreatitis and a clear history of excessive alcohol consumption. Nearly all cases show pancreatic calcifications, and about a third have glucose intolerance (endocrine pancreatic insufficiency). In children, most cases of pancreatic insufficiency are found among patients with well-established cystic fibrosis. Even in the few cases of malabsorption in which there is no clear antecedent history of pancreatic or intestinal disease, routine laboratory tests may suggest a distinction between pancreatogenous and intestinal malabsorption. For example, multiple vitamin deficiencies, hypoprothrombinemia, hypocalcemia, iron deficiency and hypoalbuminemia are rare in pancreatogenous but common in intestinal malabsorption.[12] In short, the clinical presentation often suggests pancreatogenous malabsorption with some certainty—so much certainty, at times, that UCLA housestaff and their attending physicians are content to treat about a third of adults with pancreatic insufficiency on a presumptive diagnosis alone.

The concept of diagnosis by therapeutic trial with orally given pancreatic enzymes is also popular at UCLA. Presumably, the diagnosis is supported if the patient ceases to have diarrhea and

gains weight on a regimen of these medications. This behavior by physicians indicates a reluctance to embark on time-consuming tests when the diagnosis seems so obvious and when enzyme replacement therapy is perceived to be simple and universally effective in treating pancreatic insufficiency.

It is understandable that many physicians would not wish their patients to spend a minimum of four days in the hospital for a 72-hour fecal fat collection and a secretin or Lundh test to establish a relatively obvious diagnosis. Nevertheless, diarrhea and weight loss are each fairly common among alcoholic persons, so their combination with calcific pancreatitis does not necessarily signify pancreatogenous malabsorption. Nonspecific diarrhea may spontaneously remit, whereas fixed regimens of pancreatic enzymes given orally are rarely effective in completely eliminating malabsorption; end points of therapeutic trials are therefore clouded. Unfortunately, a mistaken diagnosis of pancreatic insufficiency in these settings unnecessarily commits the patient to a burdensome, lifelong treatment.

In the case of clinically apparent pancreatic insufficiency (usually in alcoholic patients with chronic pancreatitis), simply documenting steatorrhea would eliminate treating nonspecific diarrhea with orally given pancreatic enzymes. A microscopic examination of the feces with or without a Sudan III stain for fat will identify cases of severe steatorrhea; however, accuracy is poor when malabsorption is mild.[13,14] Triglyceride ^{14}C breath tests likewise are noninvasive, require two to eight hours (less time with medium chain triglycerides) and may document steatorrhea. There is still some debate about the sensitivity of these breath tests in detecting malabsorption of fat.[14,15] Duodenal instillation of trioctanoin ^{14}C increases discrimination between normal subjects and patients with steatorrhea by eliminating variations in rates of gastric emptying, but the required duodenal intubation and the two hours of breath collection offer little advantage over the secretin or Lundh tests. Breath analysis after oral ingestion of triolein ^{14}C does not require duodenal intubation, yet appears to be a sensitive test (as opposed to tripalmitin ^{14}C) for detection of fat malabsorption.[14] While none of these will distinguish pancreatogenous from intestinal malabsorption, this distinction is probably superfluous in cases of obvious chronic pancreatitis. Repeating the triolein breath test with pancreatic enzymes given orally on a subsequent day may diagnose pancreatic insufficiency, if output of $^{14}CO_2$ is significantly increased by the enzymes[16]; but the required additional six hours hardly seems worthwhile in clinically obvious cases. Furthermore, I fear that day-to-day variations in gastric emptying, lipolytic efficiency of the added enzymes, metabolism and pulmonary excretion of the $^{14}CO_2$ may eventually be shown to flaw the early promising results of a two-day test like this.

What is really needed is a simple, short and specific single test capable of diagnosing pancreatic insufficiency. The dual-label Schilling test[17] and the dual-label fat tests[18] have this potential. Both of these tests compare the absorption of a nuclide-labeled, prehydrolyzed substrate with the absorption of a simultaneously ingested substrate, which is labeled with a second nuclide and requires luminal hydrolysis by pancreatic enzymes for absorption. Because both prehydrolyzed and lumininally hydrolyzed compounds are affected similarly, variations in gastric emptying, metabolism or excretion of labeled compounds should not affect the test result. The dual-label Schilling test is probably cheaper and easier to do because gamma counting is usually simpler than liquid scintillation. The problem is that neither of these dual-label tests has been applied widely enough for us to know their specificity and sensitivity.

Pancreatic function tests are not sufficiently sensitive to be effective in the diagnosis of pancreatic cancer and relapsing or chronic pancreatitis in the absence of malabsorption. Nevertheless, these tests effectively diagnose pancreatic exocrine insufficiency. In obscure cases of malabsorption, the secretin or the Lundh tests can be relied on to establish pancreatic insufficiency when it is the cause. However, in most cases of pancreatic insufficiency, pancreatic disease is clinically obvious; therefore, a less cumbersome, though equally specific, test is desired. The dual-label Schilling test holds promise of fulfilling this need.

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Medicine and Society: Do We Need a Philosophical Reconciliation?

LYNN WHITE, JR, in an article that appeared in the magazine *Science 80*,[1] suggested that the Western scientific tradition is beginning to lose public understanding and support because of the inattention of scientists to the changing interests of contemporary culture. He shows that this has happened in other times in several other cultures, and the result has been a decline of science in that culture. Much that he says about science and scientists, now and in the past, could also be true of medicine and physicians at present, perhaps because medicine is becoming more a science and physicians are beginning to think and act more like scientists. In any case there are disturbing signs that American medicine and Americian society are beginning to operate under different assumptions and that this development may not be receiving the attention it deserves. Since society is an integral part of medicine and medicine is an integral part of society, it surely stands to reason that both should be operating from a similar conceptual or philosophical base. If this is not the case then there should be prompt efforts at reconciliation.

For some time medicine has assumed that modern science is the key to medical progress and that private practice (the more nearly solo the better) with payment by fee for services rendered gives the best patient care. For some decades this was accepted by all concerned, and medical scientists and private practice both prospered. During this time society generously supported research and education in medical science and also sought to provide all citizens with access to what was termed mainstream care.

But more recently there is evidence that something has gone amiss. For instance, federal funding for research in medical science and for health professional education is being significantly curtailed. Also, the counterculture that began to develop some 20 years ago is becoming part of the dominant culture. It is less scientifically oriented than the earlier culture and is giving growing support to alternative approaches to health and health care and to alternative practice arrangements. The medical profession, through the voices of its leadership, is holding fast to its commitment to modern science and continues to advocate the traditional forms of medical practice including the traditional fee-for-service principle. One cannot help wondering whether American medicine and American society are beginning to march to different drummers—or, to put it another way, are beginning to operate under different assumptions and beliefs. If so, this is likely to have profound effects on both medicine and society because each is dependent on the other and they must act in concert if there is to be health and well-being for people.

The causes of what appears to be happening may run fairly deep. Western science is largely reductionist in concept and Western medicine is becoming the same. Much medical research concerns itself with only a tiny bit of the whole and much medical practice concerns itself with only a tiny bit of an ailing person. Specialization and subspecialization are the order of the day and are effects of reductionist science on medical practice and the medical profession. Contemporary culture, on the other hand, is becoming disillusioned to find that the promise or expectation that support of reductionist science would produce better health for all has not been fulfilled, and contemporary

society is not so sure that the model of practice being espoused by the medical profession is necessarily the best, the most efficient or the least costly. It is worth noting that the counterculture, which is contemporary and gaining ground, seems more taken with wholism than with reductionism as an approach to the problems of society and patient care. Rather than focus on the tiny bit, it is more concerned with the relationships and interactions among the tiny bits, or with what constitutes the whole and how it works and how it can be manipulated or made to feel better. This is a profoundly different kind of conceptual base for the public understanding and support of both science and health care.

As Professor White pointed out, it is a serious matter for science (or medicine) to lose public understanding or support and it behooves scientists (and physicians) to attend to changing interests in contemporary culture. All of this is not to say that medical science and practicing physicians should suddenly change their ways. It does suggest, however, that it may be time to seek some reconciliation of the conceptual basis of contemporary medicine and that of contemporary society. The differences in approach, if they continue, will become substantive and some blending of the concepts appears to be needed for the health and well-being of both medicine and society.

—MSMW

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CASE REPORTS

Refer to: Gomberg R, Hamm P, Martin A: Mucocutaneous lymph node syndrome (Kawasaki disease) in an adult. West J Med 135:406-408, Nov 1981

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
ECG = electrocardiogram
MCLNS = mucocutaneous lymph node syndrome

Mucocutaneous Lymph Node Syndrome (Kawasaki Disease) in an Adult

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MUCOCUTANEOUS LYMPH NODE SYNDROME (MCLNS), also known as Kawasaki disease, is an acute disease characterized by exanthem, persistent fever, mucous membrane reddening, enlarged cervical lymph nodes, periungual desquamation, and multiple organ or system complications. Until very recently,[1-4] mucocutaneous lymph node syndrome was considered a disease of infants and young children.[5]

Diagnostic criteria established by the MCLNS study group are based on Kawasaki's original detailed description.[5] They are (1) fever of five or more days duration, (2) bilateral reddening of the ocular conjunctiva, (3) erythema, dryness and fissuring of the lips and tongue, (4) reddening of the oropharynx, (5) reddening and indurative edema of the hands and feet and periungual desquamation, (6) generalized exanthem (appearing scarlatiniform) and (7) acute swelling of the anterior cervical lymph nodes.[6] Prolonged fever accompanied by four of the other criteria and excluding other similar diseases establishes the diagnosis. This includes negative cultures (viral, rickettsial and bacterial) and lack of response to antibiotic drugs.

Thus, MCLNS is a clinical diagnosis of exclusion. The syndrome becomes apparent over time and as other possible diagnoses are discarded. The cause remains unknown although there are autopsy data linking MCLNS to infantile periarteritis nodosa.

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Report of a Case

A 22-year-old man reported that he had generalized ache, stomach cramps, rash and difficulty in breathing. Fever began on the first day of the illness. The patient was seen by one of the authors the same day and treatment with penicillin, the antispasmodic drug Donnatal and meprobamate was begun. Because of continuing fever and symptoms he was seen in the emergency room of La Habra Community Hospital two days later. Temperature was 40.4°C (104.7°F); there was a generalized exanthem (maculopapular), edema and erythema of the pharynx; the tongue was beefy red and coated, and generalized aching had persisted. The patient was admitted to hospital at the time of the emergency room visit.

A throat culture was negative for *Streptococcus* and *Staphylococcus,* six blood cultures were negative and a stool culture showed no enteric pathogens, with *Escherichia coli* as the predominant organism. Despite therapy with multiple antibiotic drugs, fever persisted and symptoms grew worse as characterized by nausea and diarrhea; joint pains; swollen, reddened gums; dry, cracked, peeling lips; bilateral ocular conjunctivitis; reddening and induration of the palms; strawberry tongue; pharyngitis and cervical adenopathy; gastrointestinal and liver involvement; persistent fever (ten days), and desquamation of skin (late onset), including the periungual areas of the fingers.

Laboratory Data

Serial leukocyte counts were as follows: day one, 9,200 leukocytes with a differential of 78

percent polymorphonuclear neutrophils, 10 percent band neutrophils, 6 percent lymphocytes, 5 percent monocytes, 1 percent basophils and adequate platelets; day two, 8,900 leukocytes with 73 percent polymorphonuclear neutrophils, 21 percent band neutrophils, 4 percent lymphocytes, 1 percent monocytes, 1 percent eosinophils and adequate platelets; day three, 8,500 leukocytes with 47 percent polymorphonuclear neutrophils, 35 percent band neutrophils, 6 percent lymphocytes, 8 percent monocytes and 4 percent eosinophils and adequate platelets; day four, 6,300 leukocytes with 43 percent polymorphonuclear neutrophils; 41 percent band neutrophils, 5 percent lymphocytes, 6 percent monocytes, 5 percent eosinophils and adequate platelets; day eight, 10,500 leukocytes with 75 percent polymorphonuclear neutrophils, 12 percent lymphocytes, 12 percent monocytes, 1 percent eosinophils and 516,000 platelets. Hemoglobin and hematocrit values were stable. The sedimentation rate was 42 mm per hour on day seven in hospital. Analysis of urine was positive for bilirubin (2+) and urobilinogen (8 Erlich units). Follow-up analysis of urine was negative for urobilinogen and positive for bilirubin. Two heterophile tests were negative. Antistreptolysin O titer was negative, C-reactive protein was positive (1:5), liver enzyme levels remained abnormal throughout the clinical course along with prolonged prothrombin time and elevated bilirubin levels (2.6 to 4.9 mg per dl). Hepatitis antigen studies were negative and cytomegalovirus titer was negative as was VDRL. Cold and febrile agglutinin tests were negative; blood urea nitrogen levels remained normal, and direct and indirect Coombs' tests were negative. An electrocardiogram (ECG) showed nonspecific ST wave elevations. The patient was discharged afebrile, with abating symptoms but still icteric, on a regimen of 1,200 mg (four 5-grain tablets) of aspirin four times a day.[7] Because MCLNS was not suspected until late in the clinical course, earlier sedimentation rates and platelet counts were not done.

Posthospital Course

The patient has remained asymptomatic with follow-up ECG and biplanar echocardiogram showing no abnormalities. Aspirin therapy has been continued at a reduced dosage, and long-term echocardiographic follow-up is anticipated. A convalescent titer for leptospirosis was negative.

Discussion

This case and other cases in adults reported in the United States literature[1-4] show the need for family practitioners and internists to be as alert to MCLNS as pediatricians have become. Aside from the prolonged illness and associated morbidity, MCLNS has grave implications for heart and coronary artery disease occurring in the later phases—often after discharge from hospital. The cardiac lesions usually appear in one of two forms: arrhythmia with possible sudden death[8] or coronary artery arteritis with or without formation of microaneurysms.[9] The arteritis may lead to myocardial infarction or an aneurysm may rupture. Most deaths occur between days 11 and 50 of the disease. The pediatric literature shows 1 percent to 3 percent mortality secondary to cardiac complications and up to 30 percent cardiac involvement in patients with MCLNS.[8,9]

Other major systems involved are genitourological (renal), adrenal and central nervous system (CNS). CNS symptoms include irritability, meningismus and positive lumbar puncture. Cerebrospinal fluid may show 25 to 100 leukocytes per cu mm. The predominant cells are lymphocytes. Protein and glucose levels in cerebrospinal fluid remain within normal limits. Many of these complications seem related to arteritis.[10]

Therapy is aimed at preventing arteritis and cardiac complications. Acetylsalicylic acid (aspirin) in standard therapeutic dosages (80 to 100 mg per kg of body weight per day) has been effective as an antiinflammatory agent and tends to inhibit platelet aggregation. Thrombocytosis is a fairly uniform laboratory finding in MCLNS. The incidence of microaneurysm formation and coronary artery arteritis is lowest in patients treated with aspirin. Aspirin malabsorption and the need for extra-high dosage has been reported,[7] and serum levels should be followed carefully to avoid overdosage.

Corticosteroids appear contraindicated. A controlled study showed increased microaneurysm formation in patients taking corticosteroids. Aneurysms developed in 65 percent of these patients as opposed to 11 percent of those taking aspirin.[11] In some patients microaneurysms resolve spontaneously as evidenced by multiplane echocardiography; however, others have persistent lesions and may eventually require coronary artery bypass operations.

It is anticipated that MCLNS will be recognized

far more frequently in adult patients as articles such as this appear in the literature. It is essential that family practitioners and internists be able to recognize and treat MCLNS appropriately.

Summary

This is one of the rare reports in the United States literature of an adult with mucocutaneous lymph node syndrome (Kawasaki disease), an increasingly common pediatric problem. It is anticipated that MCLNS will be reported with increasing frequency in the adult population as family practitioners and internists become more familiar with this syndrome. MCLNS is of significance because of a 1 percent to 3 percent mortality resulting from cardiac complications of coronary artery arteritis, arrhythmias, coronary artery microaneurysm formation and prolonged morbidity.

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Refer to: Rittenberg GM, Korn JH, Schabel SI, et al: Rapid osteolysis in pancreatic carcinoma. West J Med 135: 408-411, Nov 1981

Rapid Osteolysis in Pancreatic Carcinoma

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THE BONY MANIFESTATIONS of pancreatitis are usually related to ischemia. Circulating lipolytic and proteolytic enzymes may produce endothelial damage and vascular compression, which may occlude vessels with resultant ischemia and infarction.[1-6] When vascular compromise occurs in the shaft of bones, medullary infarcts are produced; when it occurs at the end, aseptic necrosis of articular surfaces results. We present a case of rare bony manifestations of pancreatic disease related to ischemia, diagnosed as rapid osteolysis in pancreatic carcinoma.

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Report of a Case

A 63-year-old black man, a chronic alcoholic, was admitted to hospital with pain and swelling of four days' duration in his right foot, accompanied by fever and shaking chills. There was no history of trauma or preceding arthritis. His right foot and ankle were swollen and tender and two nodules, 1.5 by 1.5 cm in size, were palpable on the right achilles tendon. Initial laboratory studies gave the following values: hemoglobin 9 grams, leukocyte count 9,600 per cu mm, albumin 2.2 grams per dl, serum aspartate aminotransferase 48 IU (normal less than 50 IU), alkaline phosphatase 500 IU (normal 30 to 85 IU), bilirubin 2.4 mg per dl (1.6 per dl direct), serum amylase 18,350 IU (normal 60 to 300 IU) and serum lipase 20.7 IU (normal 0.7 to 1.0 IU).

The right third metacarpophalangeal joint, initially slightly swollen, became exquisitely tender and erythematous the day after admission. Initial roentgenograms (Figure 1A), aside from soft tissue swelling, showed no abnormalities. A week after admission, however, substantial destruction was noted in the distal end of the third metacarpal and in the fifth midphalanx (Figure 1B). Fluid aspirated from the joint contained no organisms on

Gram stain and was sterile on culture. Leukocyte count was 17,700 per cu mm (79 percent polymorphonuclear neutrophils), but no crystals were observed.

During the patient's stay in hospital, the right foot became increasingly hot and tender. Initial roentgenograms showed no abnormalities aside from old healed fractures of the second and third right metatarsals (Figure 2A). However, a week following admission, roentgenograms showed substantial lytic destruction of the second through fifth metatarsals (Figure 2B). A biopsy specimen from skin overlying the destructive bone changes showed extensive metastatic fat necrosis. Liver function deteriorated, jaundice deepened and an exploratory laparotomy showed extensive adenocarcinoma of the pancreas. A palliative cholecystojejunostomy was done. The bilirubin levels gradually fell to near normal and the remainder of the postoperative course was unremarkable. However, the patient's liver function gradually deteriorated and he died four months following operation. An autopsy was carried out, which showed diffuse metastatic carcinoma of the pancreas to liver, lymph nodes and peritoneal surfaces.

Discussion

The underlying common denominator of bone changes in pancreatic disease is felt to be ischemia.[1,5] In both acute and chronic pancreatitis, elevated proteolytic enzymes may cause direct endothelial damage.[7] Lipolytic enzymes acting on intramedullary fat produce edema, elevated intra-

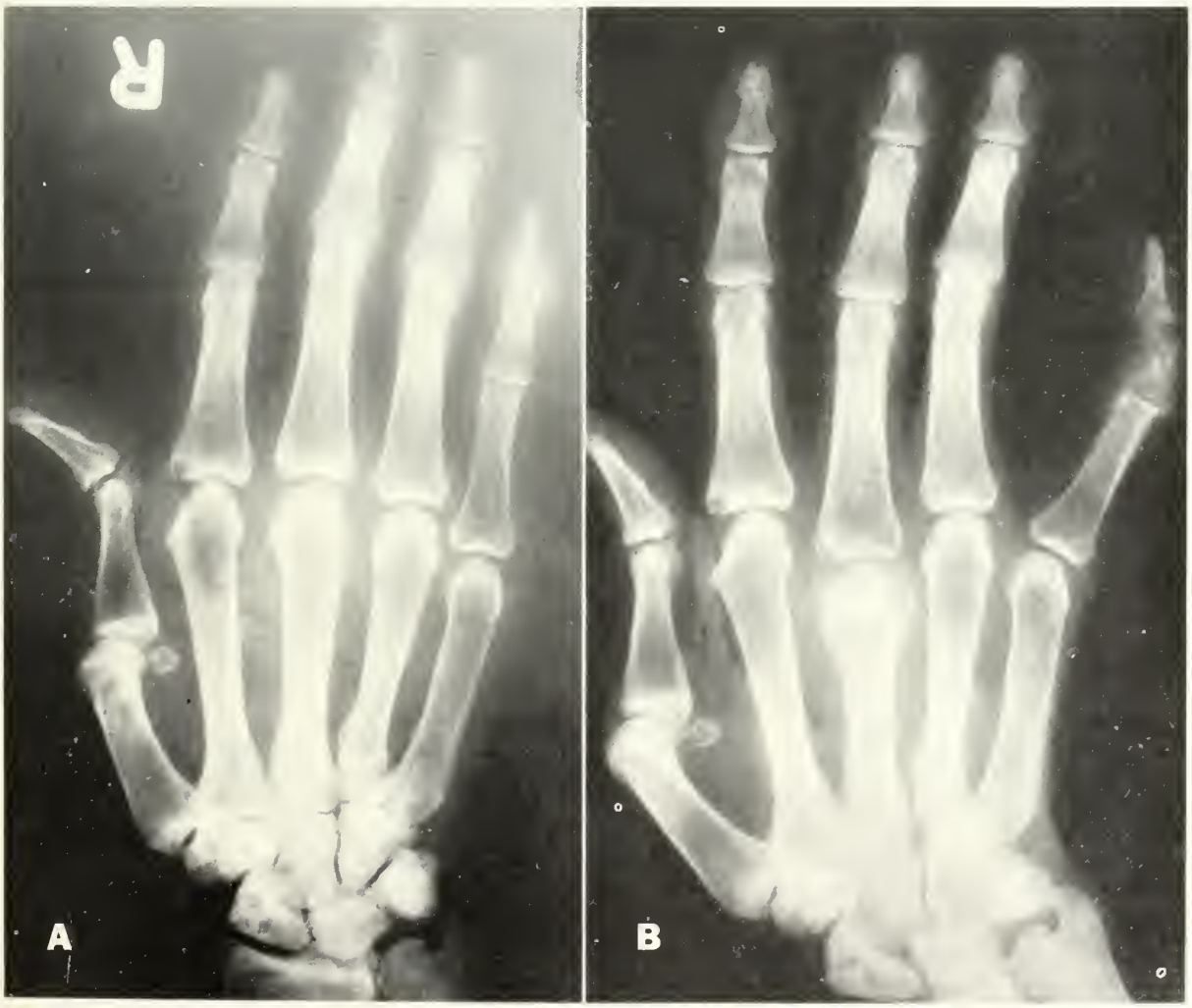

Figure 1.—**A,** Anteroposterior view of the right hand on admission showing no bony abnormalities. **B,** Anteroposterior view one week later shows destruction of the fifth middle phalanx and the third metacarpal. Note soft tissue swelling.

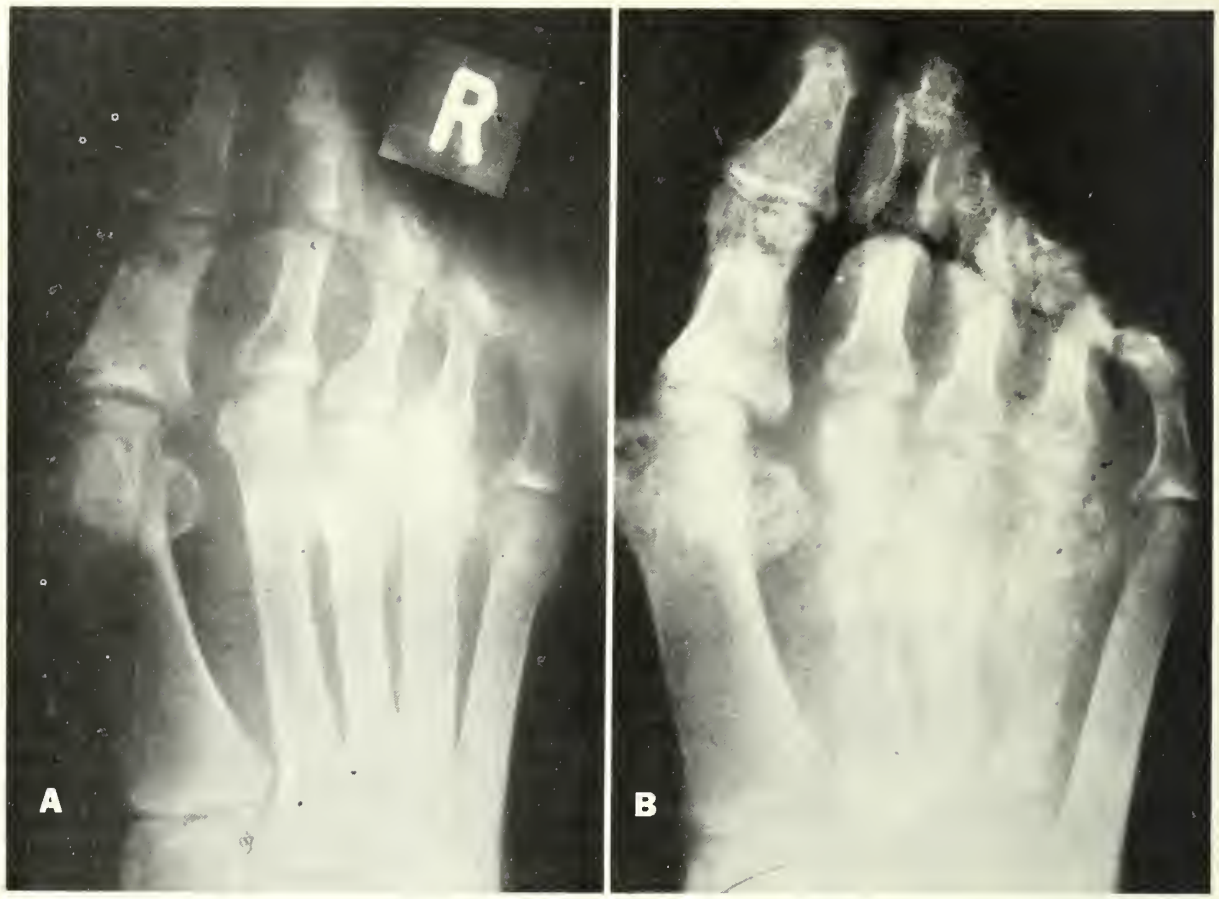

Figure 2.—A, Anteroposterior view of the right foot. There is soft tissue swelling over the metatarsals but no bony changes aside from old healed fractures of second and third right metatarsals on admission. **B,** Follow-up anteroposterior view a week later shows destruction of second through fifth metatarsals.

medullary pressure and mechanical compression on the narrow, tenuous branches of nutrient vessels, furthering the ischemia.[3,8]

Initial roentgenograms may not show abnormalities even with pronounced ischemia. With resorption of necrotic bone, however, lytic areas will appear. After several weeks calcified medullary infarcts and aseptic necrosis of articular surfaces may result.

Rapid osteolysis reflects the result of high levels of circulating pancreatic enzymes.[9] Bone dissolution may occur over a matter of days. Periosteal reaction may occur but is infrequently seen.

Skeletal metastasis is rare in pancreatic carcinoma, but when it occurs, it is usually lytic. Further, the rapid course of osteolysis should allow differentiation from the usually slow progression of metastatic disease.

Summary

Rapid osteolysis is a rare bony manifestation of pancreatic disease, usually accompanying acute or chronic pancreatitis. Rapid dissolution of bone occurs most likely as the result of high levels of circulating enzymes on already ischemic tissue and rarely accompanies carcinoma of the pancreas. A case of osteolysis involving the small bones of the hands and feet in a patient with carcinoma of the pancreas is presented.

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Refer to: Summers WK, Allen RE, Pitts FN Jr: Does physostigmine reverse quinidine delirium? West J Med 135:411-414, Nov 1981

Does Physostigmine Reverse Quinidine Delirium?

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CINCHONISM IS A SYNDROME resulting from intoxication by quinidine, cinchona alkaloids and salicylates. The signs and symptoms of the syndrome are variable and may involve any combination of the following: headaches, fever, disturbance of vision, mydriasis, decreased auditory acuity, tinnitus, nausea, vomiting, hot flushed skin, rashes, organic mental syndrome (OMS), coma and cardiorespiratory arrest.[1,p690] The organic mental syndrome may range in severity from mild memory disturbance to gross delirium. That chronic reversible dementia can be the only presenting complaint of cinchonism was reported by Gilbert.[2] Rathbun noted that acute quinidine intoxication may present as OMS without other characteristic symptoms.[3]

Cinchonism has been considered a specific phenomenon unrelated to other intoxications. We report a case of a patient in whom quinidine intoxication was reversed repeatedly by administration of physostigmine and suggest that cinchonism represents another form of acute anticholinergic syndrome (AAS).

Method

Psychiatric diagnostic methods used were those of Feighner and co-workers.[4] Organic mental syndrome is defined as a deterioration of intellectual functioning or disorientation, or both. Delirium is defined as presence of OMS plus hallucinations, delusions or agitation. Presence and severity of OMS, for a given 24 hours, in our patient was assessed by review of nursing and physician notes, with quantitation of the OMS scale (Table 1).

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ABBREVIATIONS USED IN TEXT
AAS = acute anticholinergic syndrome
DRN = drug risk number
OMS = organic mental syndrome

TABLE 1.—*Quantitation of Organic Mental Syndrome Scale*

0 = Alert, oriented and cooperative.
1 = Occasional notes of "confusion."
2 = Frequent notes of "confusion" or occasional use of soft chest restraints, or both.
3 = Constant comment on "confusion" or constant use of soft chest restraints, or both.
4 = Criteria for 1 through 3 plus comment on belligerent or combative behavior, with use of chest and extremity restraints.
5 = Criteria for 1 through 4 plus comment on delusions or hallucinations.

Exposure to psychoactive drugs was estimated by means of the drug risk number (DRN) calculation. The DRN method is described in detail elsewhere.[5] Briefly, the DRN clinically estimates total anticholinergic drug exposure, and a higher DRN indicates greater anticholinergic exposure. To calculate DRN, all drugs in a given 24 hours are grouped as follows: *class 0* includes drugs that have no known delirium-inducing or anticholinergic effects, *class 1* indicates known synergistic effect with anticholinergic agents but not known to cause delirium, *class 2* means known to cause delirium but not known at present to have central nervous system anticholinergic properties and *class 3* indicates known to cause physostigmine-reversible delirium. Having established the drug class, the dose of each drug is assigned a dosage level number. Criteria for dosage level numbers are as follows: *dosage level 1* indicates a dose range that would not have a therapeutic effect for a 24-hour period; *dosage level 2* is a dose range that would have a therapeutic effect for a 24-hour period and *dosage level 3* is a dose range that exceeds the usual therapeutic range.[5] For each drug a patient receives, the drug class is multiplied by the dosage level number. These individual drug risk numbers are summed to give a total DRN.

Report of a Case

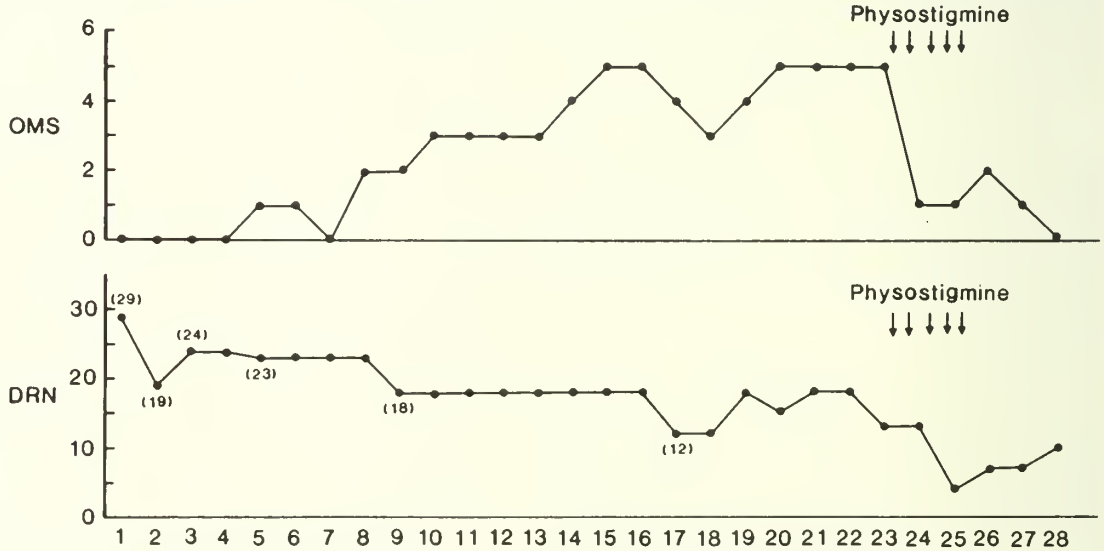
A 69-year-old man was admitted to hospital on June 19, 1975, for chest pain characteristic of myocardial infarction. One year before admission, the patient had had an inferior myocardial infarction; there was no history of additional medical or psychiatric problems in the interval. Initial and subsequent cardiac enzyme determinations

and findings on electrocardiograms were consistent with acute reinfarction of the inferior myocardium. Routine admission laboratory tests showed a slight elevation of blood urea nitrogen to 27 mg per dl and proteinuria (1 +). No laboratory data supported compromised hepatic functions.

During the first few hours in hospital, the patient survived a cardiopulmonary arrest. Ventricular premature arrhythmias following cardiopulmonary resuscitation were treated initially with lidocaine given intravenously and then with quinidine and pronestyl given orally (see Figure 1, medications and DRN). The patient did well until the fifth hospital day when he had his first brief period of "confusion." His mental status then deteriorated over the next 18 hospital days to a state of constant delirium (see Figure 1, OMS scale).

On the 23rd hospital day, psychiatric consultation was obtained. Examination of mental status showed that the patient was disoriented to time, place and person. He thought that he was a British general in the 18th century and was visually hallucinating his troops. He had paranoid delusions that the nurses were "Prussian spies and hussies" and were trying to poison him. On physical examination, mydriasis, normal retinal vasculature, mildly flushed but moist skin and ataxic gait were noted. Results of serial electrocardiograms showed development of first-degree atrioventricular block and doubling of QRS time since admission.

A presumptive diagnosis of cinchonism was made, despite unavailability of measurement of serum quinidine levels. Physostigmine, 1.5 mg, was given intramuscularly to rule out acute anticholinergic syndrome.[6,7] An hour after physostigmine was administered, the patient was mentally clear. He noted mild tinnitus and stated that he felt "like I've been in a dream." On physical examination, absence of skin flushing, increase in skin moisture, normal gait and an ability to recall three of three objects after five minutes were found. However, six hours after administration of physostigmine, the patient again showed evidence of OMS, and ten hours after physostigmine had been given, he was delirious with mild paranoid thoughts. The degree of delirium was noted by direct examination but was not severe enough for nursing comment. Administration of physostigmine a second time resulted in total clearing of mental status within an hour. On the 24th hospital



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
CLASS III																												
QUINIDINE SULFATE	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	800	200	-	-	-	-
DIAZEPAM	-	-	25	20	20	25	25	25	25	25	35	25	25	25	25	25	-	-	20	10	-	-	-	-	-	-	-	-
MEPERIDINE	50	100	150	200	50	50	50	50	-	-	-	-	-	-	-	-	-	-	-	50	-	50	-	-	-	-	-	-
PROMAZINE HCL	100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50	50	100	-	-	-	100	50	50
CHLORPROMAZINE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50	-	100	150	-	-	-	50
CLASS II																												
PROCAINAMIDE	-	-	-	-	500	750	750	750	750	750	750	750	750	750	750	750	750	750	750	750	500	750	-	-	-	-	-	-
DIGOXIN	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
HYDROXYZINE PAMOATE	50	100	150	200	50	50	50	50	-	-	-	-	-	-	-	-	-	-	-	50		50	-	-	-	-	-	-

Figure 1.—Drug regimen and course of organic mental syndrome. Dosages are given in milligrams per 24 hours. Horizontal numbers 1 through 28 represent days in hospital. (Note: Not all medications with central nervous system effect are listed.) (DRN = drug risk number; OMS = organic mental syndrome)

day, the situation was discussed with the patient's primary physician and quinidine therapy was discontinued. Physostigmine was given three more times (at approximately 12-hour intervals) in the next 36 hours, with similar clearing of recurrent delirium on each occasion. During the 26th and 27th hospital days the patient had decreasing periods of OMS, without agitation, hallucinations or delusions. By the 28th hospital day the patient was consistently mentally clear and was discharged.

Figure 1 gives the degree of OMS on a 24-hour basis and does not fully reflect the dramatic response to physostigmine. After the initiation of physostigmine treatment, soft restraints (OMS level 2) were used only once for a brief period on the 26th day. As the patient was seen twice a day by the psychiatrist, the physostigmine was given when only moderate confusion existed (OMS level 1) and appeared to be accelerating.

Discussion

The syndrome of cinchonism, especially the type presenting as OMS, is rare.[8] Data from the Boston Collaborative Drug Surveillance Program noted only six cases of cinchonism in 652 patients receiving quinidine alone (122 cases) or quinidine in combination with other antiarrhythmic agents (530 cases). All six cases of cinchonism occurred among the 122 patients who were given only quinidine. None of the six cases reported in the Boston study presented as OMS. Thus, the incidence of cinchonism without OMS was 4.92 percent of patients receiving quinidine alone and 0.9 percent of the total sample in this study. The incidence of cinchonism presenting as OMS is probably less than 1 percent.

The initial diagnosis of cinchonism appears to be correct. Our patient manifested many of the clinical signs and symptoms of classic cinchonism: nausea and emesis (days 20 through 23), headaches, transient rash (days 7 and 23), flushed skin, mydriasis, tinnitus and progressive OMS. Additionally, on serial electrocardiograms the appearance of atrioventricular block with prolonged QRS, which is consistent with type I quinidine-induced cardiac toxicity, was seen.[9] Serum assays for levels of quinidine and its active metabolites were not available from the laboratory at the time.

The diagnosis of acute anticholinergic syndrome (AAS) also appears to be correct. Persistent exposure to a pharmacological regimen with a DRN of greater than 10 is associated with delirium,[5] especially in older patients with any evidence of renal impairment.[10] From the first hospital day until the 25th day, the DRN ranged between 10 and 29 (Figure 1). Finally, repeated reversal of delirium by physostigmine therapy conclusively establishes the diagnosis of acute anticholinergic syndrome in this patient.

The administration of multiple drugs in this patient leaves some question about the role of three agents known to induce AAS (class 3 drugs). Specifically, these are chlorpromazine, promazine and diazepam.[5] Review of Figure 1 gives little support for promazine or chlorpromazine as the initial insults leading to this patient's OMS. Both were used long after the onset of delirium, appear to be used to control the patient's OMS-related agitation, and when used after mental clearing, did not reinduce delirium. The use of diazepam was temporally related to the onset of OMS (5th day); however, its reduced use between the 17th and 20th days and its discontinuance on the 21st day was not associated with clinical improvement. However, discontinuance of quinidine therapy on the 24th hospital day was temporally related to improvement. Additionally, the dosage of diazepam (5 mg three times a day and 10 mg at bedtime) is not particularly excessive. The patient also received three class 3 drugs (procainamide, digoxin and hydroxyzine pamoate). Of these three, only procainamide was given consistently throughout the course of the patient's OMS. As both procainamide and quinidine have similar anticholinergic and cardiac effects, it seems likely that procainamide was contributory here. Other drugs given to this patient but not listed in Figure 1, were Senokot (senna pod preparation), docusate (Colace), carbenicillin (Geocillin), warfarin (Coumadin) and trypsin-chymotrypsin (Chymoral).

Drachman[11] postulated that syndromes characterized by memory impairment, cognitive impairment, or both, should be considered as states of central nervous system cholinergic imbalance, and often they respond (partially and temporarily) to physostigmine. As a corollary to this view of central cholinergic imbalance as the general cause of OMS, we postulate that cinchonism is a variant of AAS as a consequence of the repeated reversal of that state with physostigmine treatment. Table 2 shows the remarkable similarity of signs and symptoms between cinchonism and acute anticholinergic syndrome.

There is other evidence that quinidine has anti-

TABLE 2.—*Signs and Symptoms of Acute Anticholinergic Syndrome and Cinchonism**

Signs and Symptoms	*Atropine Toxicity*	*Quinidine Toxicity*
Headache	+	+
Hyperthermia	+	+
Organic mental syndrome	+	+
Coma	+	+
Dry skin	+	+
Flushed skin	+	+
Blurred vision	+	+
Mydriasis	+	+
Nausea	+/0	+
Vomiting	+/0	+
Diarrhea	0	+
Constipation	+	0
Tachycardia	+	+
Atrioventricular block	+	+
Prolonged QRS	+	+
Tinnitus	0	+
Decreased hearing	0	+
Vertigo	0	+

+ = noted to occur; 0 = not noted to occur; +/0 = noted infrequently.

*Adapted from Goodman and Gilman.[1]

cholinergic properties. Miller and co-workers[12] noted that quinidine impairs formation or release of acetylcholine in peripheral neurons. Kornfeld and colleagues[13] reported that quinidine and procainamide precipitated crisis in otherwise subclinical patients with myasthenia gravis.[13] Many of the cardiac effects of quinidine are said to be due to the atropine-like properties of the drug.[1] Conversely, Bigger and co-workers[14] recently suggested that tricyclic antidepressants (with known atropinic, peripheral and central nervous system effects) could be used as long-acting antiarrhythmic drugs because of their "quinidine-like effect."

Conclusion

It seems probable that the central nervous system effect of quinidine may be mediated largely by its effects on cholinergic neurons. The repeated rapid reversals of delirium in the patient reported here supports the concept that cinchonism may be a variant of the acute anticholinergic syndrome. The authors suggest that trial of physostigmine for delirium in patients receiving quinidine alone is merited.

Summary

Cinchonism has been credited previously to a unique effect of cinchona alkaloids on the central nervous system. A case of apparent quinidine-induced delirium repeatedly reversed by administration of the anticholinesterase physostigmine is presented. It is postulated that quinidine-associated organic mental syndromes may represent another form of acute anticholinergic syndrome.

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Multiple Sleep Latency Tests During the Development of Narcolepsy

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NARCOLEPSY was first described in the late 19th century.[1] In the hundred years since this description, much has been learned about the disorder, although its pathogenesis has not yet been discovered. Four major symptoms—the narcoleptic

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ABBREVIATIONS USED IN TEXT

MSLT = multiple sleep latency test
REM = rapid eye movement

tetrad—characterize this disorder.[2] Sleepiness and associated sleep attacks are a major cause of disability[3]; cataplexy (brief loss of muscular tonus accompanying strong emotion),[4] sleep paralysis[5] and hypnagogic hallucinations[6] complete the tetrad of symptoms. Polysomnographic recordings of REM (rapid eye movement) sleep shortly after the onset of sleep (sleep onset REM periods),[7] especially with multiple daytime naps, are generally accepted as diagnostic of the disorder[8]; there is also a characteristic pattern of very short sleep onset latencies throughout the day on the multiple sleep latency test (MSLT).[9]

The peak age of onset of narcolepsy is the second decade,[2,10] and most patients describe the earliest symptoms in the pubertal years.[11] Considerable evidence exists to suggest that narcolepsy is a familial disorder.[12-17] One of the many questions that remain, however, concerns the development of symptoms and the onset of the disease. Several retrospective analyses of narcolepsy have been published recently.[18,19] Nevertheless, the onset of the illness has yet to be evaluated prospectively using polygraphic techniques. The present study reports sleep and multiple sleep latency test findings in one child in whom narcolepsy developed during the course of a longitudinal study of children who have a parent with narcolepsy.

Subjects and Methods

Seven children, each of whom has a parent with narcolepsy, were evaluated once a year for three consecutive years. These children were studied along with 19 control subjects at the Stanford Summer Sleep Camp.[20] Children came to the sleep camp in groups of three or four once each summer for at least three consecutive days. Children having a parent with narcolepsy were not identified as such to other subjects or to most staff members.

On each night, sleep was recorded from 10 PM to 8 AM using standard techniques, including an electroencephalogram (EEG) from C3 or C4, an electrooculogram from left and right outer canthi, and an electromyogram from the chin. The EEG was recorded with a low frequency cutoff of 1.0 cps and high frequency filter of 35 cps; paper speed was 10 mm per second. Recordings were scored in 30-second epochs using standard criteria.[21] Multiple sleep latency tests were given six times each day at two-hour intervals from 9:30 AM. Each sleep latency test lasted a maximum of 20 minutes. Subjects were instructed to "Please lie quietly, keep your eyes closed and try to fall asleep." The tests began when bedroom lights were extinguished. On the first day, subjects were permitted to sleep the full 20 minutes to determine if sleep onset REM periods were present. On subsequent days, tests ended after three consecutive 30-second epochs of sleep, except in cases when REM sleep was seen on the first day. In the latter cases, all subsequent tests lasted the full 20 minutes. Sleep latency test scores were computed as the elapsed time from lights out to the first 30-second epoch of sleep (sleep latency) and elapsed time from sleep onset to the first epoch of REM sleep (REM latency).

Three 60-minute performance test batteries were given daily at 10 AM, 2 PM and 8 PM. The test batteries included a 30-minute addition test,[22] a 25-word recall test[23] and a 10-minute listening attention task.[24] Alternate forms of the tests were selected at random for each testing battery. Performance test scores were averaged across each study day.

Developmental stage was determined during the second and third study years using the Tanner staging of secondary sexual characteristics.[25] Tanner staging is based on breast development and pubic hair growth in girls and on pubic hair growth and genital development in boys. Tanner stage 1 indicates prepubertal development and stage 5 is full maturation. Tanner stages from the first study year were computed using developmental norms.[26] Subjects also completed a sleep-habits questionnaire[27] at home a week before each recording session.

In this report we present findings from one of the seven children with a family history of narcolepsy and in whom signs of the disorder developed during the course of the study. When first recorded, this child was 12.2 years old, had no sleep complaints or complaints about daytime sleepiness, and had no abnormalities on physical examination. Menarche occurred at age 12, between the first and second study years. No laboratory tests were done. The child's mother had been previously diagnosed as having narcolepsy at the Stanford Sleep Disorders Clinic; this diagnosis

was confirmed with polygraphic recording of sleep onset REM periods.

Results

Table 1 lists the child's responses to selected items from the sleep-habits questionnaire completed each year, along with the percentage of children who responded similarly in a sleep-habits survey.[27] In interviews, the child never complained spontaneously about her sleep or any problems with daytime alertness nor have her parents reported any such problems. Her responses to specific items on the sleep-habits questionnaire, however, showed a progressive development of daytime sleepiness and the appearance of cataplexy, sleep paralysis and hypnagogic hallucinations.

Table 2 summarizes the nocturnal recording results of this child, averaged for the second and third recording nights of each yearly session. Appropriate Tanner stage-matched values from control subjects recorded at the sleep camp are also listed. Total sleep time increased by about 30 minutes from the first to the third year. This increase was reflected, in part, by a reduction in wakefulness after sleep onset. Slow wave (stages 3 and 4) sleep stages declined across the three years, while stages 1 and 2 increased. REM percent-

TABLE 1.—*Responses to Sleep-Habits Questionnaire*

	*Year 1 (Percent)**	*Year 2 (Percent)**	*Year 3 (Percent)**
Age	12.2	13.2	14.2
Tanner stage	2	3	4
Do you take naps?	Never (53)	Never (53)	1-2/month (4)
Do you have trouble staying awake in the mornings?	Never (47)	<1 mo (25)	Every day (3)
Do you have trouble staying awake in the afternoons?	Never (79)	Never (79)	Every day (1)
Do you actually fall asleep in school?	Never (89)	Never (89)	Every day (0)
Do you feel weak when you laugh or are angry?	Never (57)	Never (57)	<1/month (18)
Do you feel paralyzed right after you wake up?	Never (66)	Never (66)	Every day (8)
Do you have a life-like dream as you are falling asleep?	Never (31)	Never (31)	Every night (20)

*Percentages of survey subjects (218 boys and girls aged 10 to 14) who gave the same response are listed in parentheses.

TABLE 2.—*Summary of Nocturnal Sleep*

	Year 1	*Tanner 2 Controls**	*Year 2*	*Tanner 3 Controls**	*Year 3*	*Tanner 4 Controls**
Recording time (min.)	604	600 (5)	600	600 (5)	598	600 (5)
Total sleep time (min.)	544	545 (25)	563	550 (16)	575	544 (30)
Wake after sleep onset (min.)	8	8 (8)	4	10 (9)	2	16 (17)
Percent stage 1†	10	8 (3)	9	8 (2)	11	9 (2)
Percent stage 2†	39	46 (4)	52	48 (6)	50	49 (4)
Percent stages 3 and 4†	26	23 (5)	19	18 (5)	17	16 (5)
Percent REM†	25	20 (3)	20	22 (3)	21	21 (2)
REM latency (min.)	61	114 (37)	82	80 (17)	40	101 (40)

REM=rapid eye movement

*Control value standard deviations are listed in parentheses.
†Percentages are based on total sleep time.

TABLE 3.—*Summary of Multiple Sleep Latency Tests*

	Day 1		*Day 2*		*Day 3*		*Overall Mean SLT*
	*Mean SLT**	*REM Episodes*	*Mean SLT*	*REM Episodes*	*Mean SLT*	*REM Episodes*	
Year 1	14.1	0	9.0	N/A	12.4	N/A	11.8
Tanner 2 controls	18.1 (2.3)†	1/60	18.1 (2.3)	N/A	18.9 (1.6)	N/A	18.4
Year 2	10.3	0	11.0	N/A	10.0	N/A	10.4
Tanner 3 controls	16.5 (2.8)	1/60	15.7 (3.4)	N/A	16.0 (5.2)	N/A	16.1
Year 3	3.8	5/6	6.8	5/6	6.7	3/6	5.8
Tanner 4 controls	15.5 (3.3)	2/48‡	15.7 (3.4)	N/A	16.1 (3.5)	N/A	15.8

N/A=not applicable; REM=rapid eye movement; SLT=sleep latency test.

*SLT values in minutes.
†Standard deviation for control values given in parentheses.
‡One REM episode in two subjects. No control subject had two REM episodes on the multiple sleep latency test.

ages showed a decline from the first to the second year but stayed approximately the same in year 3. These sleep-stage findings were comparable to those of the control subjects at the same Tanner stages and recorded under identical circumstances. Latency to REM sleep was below these norms in the first and third years. The very low average REM latency in year 3 reflects an abnormally low (four minutes) REM latency on the third recording night.

The multiple sleep latency test results are summarized in Table 3, where the results are compared with mean values of control subjects matched for Tanner stage. In the first and second study years, the mean sleep latency test scores of this child were lower (sleepier) than controls on each study day; however, she had no episodes of REM sleep onset in either of the first two years. In the third study year, the child was much sleepier than in either of the first two years and significantly sleepier than controls. REM sleep episodes were seen in 13 of 18 sleep latency tests in the third study year, as compared with only one REM sleep episode in each of two Tanner stage 4 control subjects. Finally, no episodes of cataplexy were observed in this child.

Performance test scores showed no impairment of this child in any of the three study years. Each year her performance was within the range of matched control subjects.

Discussion

According to the criteria of investigators using recording techniques[8,28] similar to those employed in the present study, the presence of two or more sleep onset REM periods in multiple sleep latency tests establishes the diagnosis of narcolepsy. Thus, this study represents the first detailed prospective polygraphic assessment of sleep and sleepiness in the development of narcolepsy, suggesting that such evaluations are possible by recording children with a family history of narcolepsy.

A key issue is the prospective assessment of relative risk for offspring of patients with narcolepsy. In the present case, two possibly predictive signs were apparent before symptoms were reported and before sleep onset REM periods developed. These were an abnormally low latency to REM sleep shown on nocturnal recordings done at Tanner stage 2 and an abnormally high propensity to fall asleep shown by the multiple sleep latency tests. Clearly, no conclusions can be drawn on the basis of a single case. (Two of the six other narcoleptic offspring remaining in the study have had these two signs. One boy at Tanner stage 2 had an average REM latency of 71 minutes and average MSLT score of 15.9 minutes. A girl at Tanner stage 4 had a REM latency of 51 minutes and an average MSLT score of 11.4 minutes. Both are still within the age of risk for developing the disorder. Nevertheless, until additional data are obtained, speculation is premature.)

The usefulness of the multiple sleep latency test as a diagnostic tool for narcolepsy[8,28] has been supported in this study. In this case, the only nocturnal sleep onset REM period was seen in the final recording night. On the other hand, sleep onset REM periods occurred consistently on three or more sleep latency tests each day of the third study year.

The child's reports of symptoms are impressive because they parallel the polygraphic findings but less impressive when compared with control responses (Table 1). Clearly, this child's reports of sleepiness are more severe than those of other children; however, quite a few children gave similar responses to the questionnaire items regarding cataplexy, sleep paralysis and hypnagogic hallucinations. When interviewed, the child reported very few episodes of clear-cut cataplexy. The relationship in adult patients between the occurrence of auxiliary symptoms, especially cataplexy, and sleep onset REM periods has been emphasized by Dement.[3] In this case, cataplexy was the least frequent symptom reported, yet sleep onset REM periods were a well-established pattern. We have recorded sleep onset REM periods in one other child (16 years old) of a narcoleptic parent who complained of sleepiness and none of the auxiliary symptoms.[24] Guilleminault[4] reported a similar finding in a young woman seen early in the development of the illness. These findings suggest that childhood or adolescent narcolepsy—as defined by an abnormal latency to REM sleep—can be diagnosed in children who may not have the classic clinical syndrome.

In the third study year, when the child was permitted to sleep longer during the multiple sleep latency tests on days 2 and 3, there was no evidence of a change in nocturnal sleep that could be attributed to the additional napping. The reduced number of REM episodes on the third study day may have been related to the longer naps on days 2 and 3; however, this relationship is not established.

In the evaluation of daytime sleepiness in con-

trol subjects,[20] we have seen a clear relationship between pubertal development (Tanner stage) and increased daytime sleepiness in the absence of any changes in total nighttime sleep. Multiple sleep latency test scores showed a significant increase in daytime sleepiness at Tanner stages 3 and 4. From these data we have hypothesized that this period of maturation might be a particularly vulnerable stage in the development of narcolepsy. In the present case the signs and symptoms of narcolepsy were first seen at Tanner stage 4, supporting this hypothesis. The findings in this case suggest the possibility of an additive effect wherein a preexisting tendency toward daytime sleepiness and the pubertal augmentation of sleepiness lead to an unequivocally pathological level of sleepiness.

Summary

A 12-year-old girl whose mother has narcolepsy was evaluated with sleep-habits questionnaires, Tanner staging, nocturnal sleep recordings and multiple sleep latency tests at yearly intervals for three consecutive years. In the first year the child reported no symptoms of narcolepsy. In the third year all symptoms were present. Nocturnal sleep recordings showed reduced REM latencies in years 1 and 3, with one sleep onset REM period in year 3. Results of multiple sleep latency tests each year showed an excessive tendency to fall asleep; however, abnormally short REM latencies were not seen until year 3. Sleep onset REM periods were seen on 13 of 18 sleep latency tests in year 3. The signs and symptoms of narcolepsy developed when the child was at Tanner stage 4.

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A Prolonged Severe Intoxication After Ingestion of Phenytoin and Phenobarbital

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THE ANTICONVULSANT DRUGS phenytoin and phenobarbital are often prescribed concomitantly in the treatment of epilepsy. Despite this association, few cases of severe combined overdose with these agents have been reported. Further, cases of fatal

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poisonings with phenytoin alone are rare in the literature.[1-3] In the case reported here, that of a woman without epilepsy, there was delayed absorption and prolonged severe toxicity after combined phenytoin and phenobarbital ingestion.

Report of a Case

A 22-year-old mentally retarded woman, who was not epileptic and who had been in good health previously, was brought to the University of California Davis Medical Center emergency room on August 22, 1980. The patient said she had taken an unknown amount of phenobarbital and phenytoin, which belonged to a friend, earlier in the day. On examination, the patient was noted to be lethargic but was able to answer questions. Vital signs were as follows: temperature 37°C (98.6°F), blood pressure 104/58 mm of mercury, pulse 96 beats per minute and respirations 12 per minute. Nystagmus was notably absent. The rest of the physical examination findings were unremarkable. The initial laboratory examination showed normal values for electrolytes, glucose and blood urea nitrogen. The leukocyte count was 9,200 per cu mm, with a hemoglobin of 14.7 grams. A blood drug screen showed a trace of either tolbutamide or chlorpropamide, a small amount of caffeine, and phenobarbital and phenytoin levels of 15 and 18 mg per liter, respectively. Phenobarbital and phenytoin were measured in serum using high-performance liquid chromatography.[4] Confirmation of serum results was made by gas chromatography.[5] Initial treatment consisted of gastric lavage with more than 3 liters of normal saline followed by administration of activated charcoal and magnesium citrate. No pill fragments were recovered.

The patient was evaluated by a psychiatrist and then observed for several hours without change in her status. Because of an outstanding warrant, she was discharged to jail. While incarcerated and after being searched, the patient was noted to become extremely agitated over the next day. She was returned to the emergency room almost 24 hours after her first visit for reevaluation. On physical examination, she was afebrile with vital signs as follows: blood pressure 110/60 mm of mercury, heart rate 88 beats per minute and respirations 20 per minute. She was agitated and disoriented with lateral gaze nystagmus. Serum values for electrolytes and glucose were normal. A urine screen for phencyclidine was negative. A repeat blood drug screen showed only phenytoin

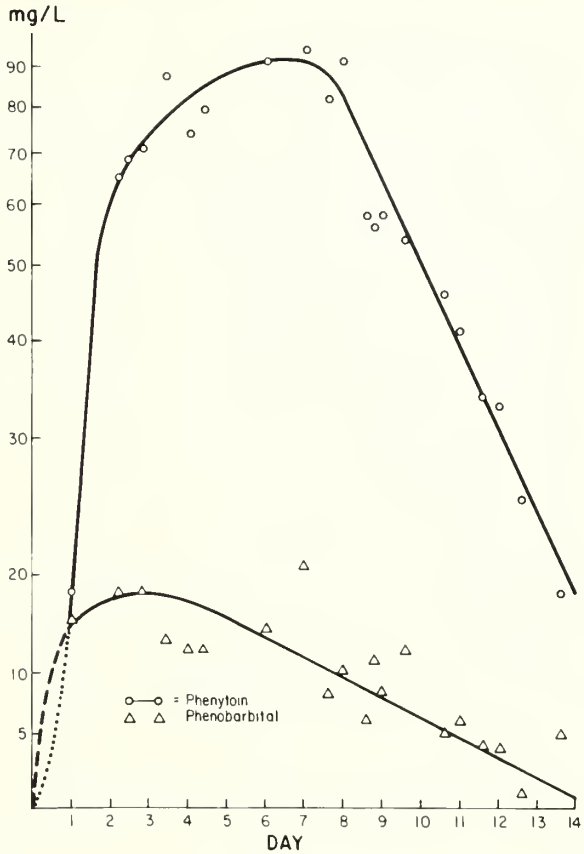

Figure 1.—Serum levels of phenytoin and phenobarbital are plotted against days in hospital. The initial presentation to the emergency room is considered day 1. Solid lines represent an approximate best fit, and the broken lines represent estimated curves.

(65 mg per liter) and phenobarbital (18 mg per liter). An electrocardiogram showed sinus tachycardia with diffuse nonspecific ST-T wave changes. Arterial blood gas determinations while the patient was breathing 2 liters of oxygen were as follows: oxygen pressure (P_{O_2}) 97 and carbon pressure (P_{CO_2}) 31 mm of mercury, and pH 7.32. The patient received magnesium citrate a second time and was admitted to hospital.

The serum levels of phenytoin and phenobarbital and the patient's clinical course are summarized in Figure 1 and Table 1, respectively. The patient became less agitated and more lethargic as phenytoin serum levels increased. On the third hospital day, a barium swallow test was done, which showed no evidence of retained pills. By the sixth and seventh days, the patient was comatose, with disconjugate gaze, decreased deep tendon reflexes and absent gag reflex. Nystagmus was not noted. Because of the increase in serum levels of phenytoin, the patient was given mag-

TABLE 1.—*Hospital Course and Neurological Status of Patient Following Combined Phenytoin and Phenobarbital Ingestion*

	*Hospital Day**													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Hospital course														
Gastric lavage	x†	..	..	..	..	..	..	..	..	..	..	..	..	..
Charcoal	x	..	..	..	..	x	x	x	..	..	..	..	..	..
Magnesium citrate	x	x	..	x	..	x	x	x	..	..	..	..	..	..
Elevated temperature	..	..	..	..	..	..	x	x	x	..	..	..	..	..
Cephalosporin	..	..	..	..	..	..	x	x	x	x	x	x	..	..
Lactic dehydrogenase (units/liter)	207	275	233	242	223	..	399	387	..	..	..	268	..	..
Serum aspartate aminotransferase (units/liter)	28	32	31	33	32	..	54	121	..	..	..	31	..	..
Total bilirubin (mg/dl)	0.5	0.4	0.4	0.4	0.4	..	0.4	0.2	..	..	..	0.2	..	..
Albumin (grams/dl)	4.6	4.3	4.2	4.1	4.1	..	4.0	3.6	..	..	..	3.7	..	..
Neurological status														
Coma	..	..	..	..	x	x	x	x	..	..	..	..	..	..
Agitation	..	x	x	..	..	..	..	..	x	x	x	x	..	..
Ataxia	x	..	..	x	..	..	..	..	..	..	..	..	x	..
Nystagmus	..	x	x	..	..	..	..	..	x	x	x	x	x	..

*The initial presentation to the emergency room is considered day 1.
† x indicates that on a given day the procedure was done, the drug was given or the symptom was noted.

nesium citrate on day 4 followed by three additional doses of charcoal and magnesium citrate on days 6, 7 and 8.

On the seventh day a fever developed. Blood cultures were negative; however, urine culture grew more than 100,000 colonies of *Enterococcus*. The patient defervesced during antibiotic treatment over the next 48 hours. On day 9 the patient's serum phenytoin levels began to fall, which was accompanied by a return of nystagmus and agitation. Liver function tests gave only minimally elevated results by day 9 (Table 1). She continued to improve neurologically as serum phenytoin and phenobarbital levels decreased. The patient was discharged 14 days after she had ingested the drugs. She was oriented and without nystagmus.

Comment

This case represents a unique demonstration of severe phenytoin intoxication after combined phenytoin and phenobarbital ingestion. Extremely slow absorption of phenytoin was observed with peak serum levels not attained until the seventh hospital day. This delay occurred despite gastric lavage and the administration of activated charcoal and cathartics on the day of ingestion. Most previous reports of phenytoin toxicity have reported levels that declined from the initial serum determination.[6-9] Two patients[10,11] were found to have a prolonged plateau phase followed by a slow decline phase in serum levels. One of these cases[11] involved an alcoholic man with a history complicated by gastrectomy and chronic anticonvulsant therapy. The patient presented with a phenytoin level of 64 mg per liter and a phenobarbital level of 63 mg per liter. There was no mention of emesis, gastric lavage or activated charcoal administration in the case report. The only other reported case of prolonged phenytoin levels occurred in a 6-year-old child despite treatment with emesis, gastric lavage and administration of activated charcoal and cathartics.[10] A single report observed phenytoin levels that continued to increase after ingestion.[12] A 5½-year-old boy accidentally received 500 mg a day of phenytoin and 100 mg a day of phenobarbital for approximately 20 days while in hospital. An initial phenytoin level of 85.2 mg per liter was obtained three hours after the last dose. This rose to 108.5 mg per liter 24 hours later but rapidly decreased over the next three days.[12]

The rise in serum phenytoin levels that occurred in our case can best be explained by decreased gastrointestinal motility, which prolonged the time available for absorption. Because our patient was searched and incarcerated in isolation, we feel comfortable that she had no further opportunity to ingest phenytoin and phenobarbital. The barium swallow test done on the third day failed to show any evidence of pill bezoar or gastric-outlet obstruction. This reduces the likelihood of any serious gastric retention of pill fragments. Although a significant enterohepatic-loop exists, it

is the pharmacologically inactive hydroxylated metabolite of phenytoin that is reabsorbed after bacterial deconjugation, and this compound would not contribute to the rise in serum levels seen in this patient.[6,13] Wide variation in the rate of phenytoin absorption have been reported.[14-16] In healthy volunteers given a single dose of 900 mg of phenytoin by mouth, the time to reach peak plasma levels varied from six to eight hours.[16]

Peak phenytoin levels obtained in this patient are consistent with levels reported in previous cases of severe poisoning and intoxication.[3,6-12] Laubscher[3] reported a fatal case of pediatric phenytoin ingestion with an initial serum level of 94 mg per liter. The level had decreased to 45 mg per liter at the time of vascular collapse and death. In contrast, phenytoin levels of 89 mg per liter have been associated with only minimal neurological findings in some patients.[17] This variability in response to serum levels was less pronounced in a large series of phenytoin-intoxicated patients.[18] Kutt and co-workers[18] found that phenytoin levels of 20 to 30 mg per liter were associated with nystagmus, 30 to 40 mg per liter led to ataxia and levels greater than 50 mg per liter progressed to further mental changes and coma. The increased side effects of phenytoin seen in patients with hypoalbuminemia are thought to be a result of increased circulating unbound phenytoin in these patients.[19] Booker and Darcey[20] have noted a closer correlation with free or unbound phenytoin levels and clinical intoxication. As can be seen in Table 1 and Figure 1, the neurological findings correlated with the total serum levels in our patient both during the ascending and descending phases. However, a small decrease in serum albumin and possible phenobarbital-binding competition complicates estimation of unbound phenytoin in this patient.

The few cases in the literature that report simultaneous phenytoin and barbiturate ingestion do not address their potential interactions.[8,11,21] Phenobarbital is both a known inducer of the enzymes that metabolize phenytoin and a competitive inhibitor of the same enzymes.[22] The effect of phenobarbital on phenytoin levels is varied. Kutt[22,23] has reviewed several clinical studies with therapeutic doses of each drug and concluded that the balance between the stimulating and inhibiting effects of phenobarbital on phenytoin metabolism is difficult to predict for the individual patient. Genetic variability in phenytoin metabolism has been shown[24,25] and may play an important role in the phenobarbital-phenytoin interaction in any individual toxic patient.

The elimination half-life ($T_{1/2}$) of approximately 96 hours in this patient is substantially longer than the average $T_{1/2}$ of 22 hours (range 7 to 55 hours) seen in healthy volunteers given therapeutic doses.[26] Patients with phenytoin intoxication have been reported to have a wide spectrum of $T_{1/2}$ values varying from 24 to 230 hours.[9-11] The wide range of $T_{1/2}$ values is in part due to the probable continued absorption and saturation kinetics seen with toxic serum levels. Metabolite or product feedback inhibition has not been conclusively shown in humans.[27]

Several authors have questioned the use of hemodialysis in the treatment of acute phenytoin overdoses.[10,28] The few case reports in which successful hemodialysis or peritoneal-dialysis has been described do not provide adequate documentation of clinical benefit or significant recovery of phenytoin in the dialysate.[21,28-31]

In a recent review of one hospital's drug-related hemoperfusions, phenytoin was not one of the "severe" cases of drug intoxication treated with this technique.[32] Lorch and Garella[32] stated "in view of the low morbidity and mortality observed in our patients we cannot support the widespread use of hemoperfusion for most common intoxicants." Certainly this is true for most moderate and severe phenytoin intoxications.

This case shows that significant absorption of phenytoin can occur despite emesis, gastric lavage, and treatment with activated charcoal and cathartics at first presentation. Thus, efforts should be focused on supportive care and the prevention of further absorption of phenytoin. Repeat administration of both activated charcoal and cathartics may be necessary to prevent the prolonged and delayed absorption seen in this case.

Summary

A 22-year-old nonepileptic woman ingested an unknown amount of phenytoin and phenobarbital. Peak serum levels of 95 and 21 mg per liter for phenytoin and phenobarbital, respectively, were observed seven days after gastric lavage, charcoal and cathartics had been administered. Blood levels of phenytoin began to decrease only after repeat multiple doses of charcoal and cathartics were given. An elimination half-life of approximately 96 hours for phenytoin was found. The prolonged

phenytoin toxicity seen in this case is probably secondary to delayed intestinal absorption and to saturation kinetics seen with toxic serum levels leading to the long phenytoin elimination $T_{1/2}$. Therapeutic efforts in cases of massive phenytoin ingestion should be focused on supportive care and the prevention of further phenytoin absorption with repeat administration of activated charcoal and cathartics.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Fatalities from Motorcycle Accidents

To the Editor: In their article in August on the role of helmets in reducing head injuries from motorcycle accidents,[1] Luna, Copass and Oreskovich conclude in part that "the death rate for those with and without helmets was not significantly different." However, they only studied motorcycle accident victims who came to the hospital emergency room. Unless their statement, "of the fatalities listed, there were no pronouncements of death at the scene," also includes all who died at the scene, perhaps their conclusions should be more limited. It is possible that the difference between their observation and that of others lies in the fact that most motorcycle accident victims who die of head injuries die at the accident scene.

MAX BADER, MD
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Health Division
State of Oregon Department of Health Resources
Portland

REFERENCE

1. Luna GK, Copass MK, Oresrovich MR, et al: The role of helmets in reducing head injuries from motorcycle accidents: A political or medical issue. West J Med 135:89-92, Aug 1981

* * *

Dr. Luna Replies

To the Editor: This is in response to Dr. Bader's inquiry regarding the validity of our conclusion ". . . the death rate for those with and without helmets was not significantly different." First, as stated in our article, there were no pronouncements of death at the scene. All accidents within the city of Seattle in which emergency personnel —that is, firemen or paramedics—were called were included in our series. Although city police have the authority to pronounce patients dead at the scene without involvement of firemen or paramedics, this is not done. The organizational efficiency and skills of the paramedics in the Seattle area definitely contribute to the relatively low mortality rate in our study. Resuscitation attempts including establishment of a tracheal airway, intravenous administration of fluids, external cardiac massage, flutter valve thoracostomy, pericardicentesis and pharmacological cardiac support were all utilized when necessary.

It would be fallacious to interpret our results and conclusions as proof that helmets are of no value to a motorcyclist involved in an accident. Instead, our results indicate that it is the overall force impacted to the rider's body during an accident that determines mortality.

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The Politics of Helmets for Motorcyclists

To the Editor: Dr. Luna and his co-workers have done a fine job in their article[1] in the August issue of demonstrating once again that the use of helmets will reduce severe head injury and long-term neurological defects from motorcycle accidents.

Even in the face of such dramatic evidence, motorcycle owners still feel that it is their right as citizens to risk serious injury if they choose. Society on the other hand is forced to pay part or all of the medical expenses incurred in such accidents and to provide welfare assistance for the victims of severe neurological injuries. These costs are enormous and the funds could be spent on social programs that would benefit the entire society rather than on one unfortunate and not too bright individual.

One way to solve the dilemma of the rights of the individual versus the rights of society would be legislation requiring proof of a substantial insurance policy (1 to 2 million dollars) for those persons who wish to ride without helmets. Proof of ownership of such a policy would allow the rider to pursue his individual right to highway roulette without interference by the state.

At the same time, society would be protected from having to bear the costs of his recklessness.

MARCUS A. CONANT, MD
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REFERENCE

1. Luna GK, Copass MK, Oreskovich MR, et al: The role of helmets in reducing head injuries from motorcycle accidents: A political or medical issue? West J Med 135:89-92, Aug 1981

* * *

TO THE EDITOR: I am writing in response to the article, in the August issue of the journal, entitled "The Role of Helmets in Reducing Head Injuries From Motorcycle Accidents: A Political or Medical Issue?"

This syllogism would make Karl Marx proud:

Fifty-nine percent of the unpaid medical bills are borne by taxpayers.

Motorcycle helmets reduce head injuries.

Therefore, since society is financially responsible for an individual's health, prerogatives should be replaced by a law mandating helmets.

Who says doctors are against Socialized Medicine?

ALAN H. WALTHER, MD
San Diego

Motorists, Seat Belts and Individual Freedom

TO THE EDITOR: Luna and co-workers contribute proof that the use of helmets by motorcyclists is medically advantageous.[1] The accompanying editorial by Dr. Trunkey[2] adds pertinent societal and economic arguments for requiring all motorcyclists to wear helmets. However, the probable benefit from universal helmet usage by motorcyclists pales to virtual insignificance when compared with the savings in lives, suffering and dollars that could be achieved if seat belts (with shoulder harnesses) were universally worn by motorists. The loss of "individual freedom" to a motorist who is required to wear a seat belt is, if anything, less than a cyclist's loss from a mandatory helmet, and the advantage (collectively) to society is greater. Thus, it seems inappropriate to require motorcyclists to practice self-protection unless we are willing to require automobile drivers and passengers to do likewise.

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The Face of Medicine

Medicine has a changing and unchanging face, and it is as necessary to learn the meaning of the first as it is to recognize and cherish the second.

Sir F. M. R. Walshe[1]

One wonders if the young doctor of today, as he emerges from the protective womb of his residency training, gives a moment's thought to what tremendous changes have come about in the medical world he is now entering?

Does he realize that medical practice now is at once more difficult, yet simpler, thanks to third parties and technology; that his colleague of a generation or two ago dealt more with the art of medicine but less with the bureaucracy?

That the good old family doctor enjoyed the intimacy of the house call when sometimes his best and only medicine was a cool hand on a fevered brow, yet that he was denied the comfort of the weekend and nighttime coverage in the ER, as we have it now?

Surely this young doctor would be appalled by the ulcer treatment of yesteryear—those horrible Sippy powders and sickening half-and-half, round the clock, on the hour. Now the ulcer, by fiberoptics seen, quickly gets a prescription for an antacid and cimetidine.

And the GI surgeons of today may never know the joy (or the tedium) of the three layer anastomotic closure—so meticulous, as he pops in an instant row of staples—so simple, yet miraculous.

The dermatologist of not too long ago had only coal tar, sulfur, aquaphor and salicylate. Now he just decides whether therapy shall be methotrexate, hydrocortisone or fluorinate.

The heart doctor of that bygone era used a stethoscope to listen and his fingers for percussion; now he depends on ultrasound, telemetry, echocardiography, in making his decision. For HBP and CHF old timer had phenobarb, dig, salts of mercury—little more; today we are blessed with dozens of diuretics, methyldopa and beta blockers galore.

The stork's assistant of another year was a cross between midwife and accoucheur. His teachers Simpson, Scanzoni, DeLee and Deaver; his greatest foes, bad lochia, milk leg, childbed fever. Today's sophisticated OB's fear less the dangers of infection thanks to antibiotics and quick C-section, than they fear malpractice, "wrongful life," endless litigation.

Yes, the face of medicine is surely changing, and we have come to learn that meaning. Yet the unchanging face of medicine won't fade away—the patient continues as "number one," the term "*my* doctor" is here to stay.

E. R. W. FOX, MD
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REFERENCE

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Fibrositis

TO THE EDITOR: The notion that fibrositis (and its verbal cousins) is a "disease" has been buried time and again through demonstrations that histological, biochemical, constitutional and electrical alterations are absent. At best the term (or terms) refers to multiple complaints of skin, muscle, tendon and bone tenderness. An article by Bennett in the May issue[1] attempts to exhume the concept and to give it substance by drawing on distantly relevant studies on sleep, enkephalins and the gate theory of pain which Bennett hopes —eventually—may contribute to the legitimacy of fibrositis as a "disease." Additionally, he includes the enzymic hypothesis of fibrositis (interstitial myofascitis) of Awad and co-workers[2,3]; this loosely spun and fenestrated theory remains isolated and unverified and has been critically examined and discounted.[4]

But if such a disorder as fibrositis can be shown to exist, then Bennett prefers to call it nonarticular rheumatism. Does such verbal juggling add insight or understanding especially when the author describes in detail the psychological features that accompany and apparently underlie the multiple complaints of these patients? Bennett also informs us that similar features are noted in a condition termed psychogenic rheumatism. This latter term—for which Bennett is not responsible —was invented by earlier writers who liked to breed verbal chimeras that suggested simultaneously both organic and nonorganic processes.

Nonetheless, Bennett displays the fibrositic nodule as the centerpiece of evidence for fibrositis; it was once thought to result from unknown inflammatory processes—a notion now exploded. Bennett concedes that histologists have found the nodules to be nothing more than fat extruded through fascial rents or nerve openings. For a second supposition, he offers localized muscle spasms as an explanation for the nodules although such has long eluded the combined search of myologists and pathologists.[4] The so-called "trigger points"—TP's to their familiars—provide the second diagnostic pillar of fibrositis. By means of an elaborately tangled web of neurophysiological speculations reinforced by repetitious assertions,[5] pure theory is transmogrified into apparent facts or "factoids." Consequently, the sore spots at muscle-tendinous insertions are being attended by all kinds of therapies including injections of procaine or cortisone, or both. Trigger points, however, are easily demonstrated in healthy army recruits[6,7] but are, of course, only treated in complaining subjects. That small injections of normal saline solution and even dry needling do as well is seldom mentioned, perhaps because they smack of witch doctoring.

Why then is there reluctance to discard this enigmatic diagnosis? Is it because there are firmly placed and vested medical and legal interests that wish to perpetuate it and particularly those who treat and litigate its illegitimate offspring of the rear-end collision (traumatic) fibro(myo)sitis? Indeed, I am at a loss to understand what Dr. Bennett is trying to say. Is it that fibrositis is really a psychological disturbance but one which *uniquely expresses itself* through the appearance of nodules, muscle hardenings and trigger points, or is it that benign muscle soreness, nodules, pain and so forth ought to have a special name, class and therapy when complexed with psychological morbidity? I ask this because implicit in Dr. Bennett's article is the idea that fibrositis should be thought of as a product of psychic stress or distress, although he prefers not to state it overtly.

Many writers on the subject show a disinclination, indeed a strong aversion, to calling fibrositis what it most appears to be: a psychophysiologic state. Preferably, attention is directed toward sore spots, tender lumps, painful skin folds, aching bones and other peripheral distractions. This latter approach evidently suits many patients for whom it does not matter whether a cure is achieved; indeed, open-ended and long-term

therapy that does not threaten the patient with a cure often appears to be the unexpressed attraction to the program. Names, prefixes, suffixes and adjectives create disease entities which then take on a life of their own, conjugate among themselves and end up with strange hybrids in which the ancestral features are obscured. Fibrositis (and its many nominal forebears and descendants) represents an example of how the common aches, pains, sorenesses—and sorrows—of humankind are, through naming, established as disease entities. Is this medical progress?

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* * *

Dr. Bennett Replies

To the Editor: Like Dr. Weinberger, there are many physicians who regard fibrositis as a "psychophysiologic state." That term itself is merely another example of "verbal juggling" and may ease the diagnostic conscience, but it does little to ease the patient's suffering. It is easy to dismiss a patient whose pain cannot be readily explained as a *crock;* it certainly saves the physician time and nervous energy, for the patient goes elsewhere. Pain is, of course, a purely subjective sensation; we have no way of measuring it effectively. There is no evidence that patients who have pain of a psychogenic origin suffer any less distress than those who have a well-defined cause for their pain—to think otherwise is pure arrogance.

One major advance in studying patients with fibrositis has come from the work of Smyth and Moldofsky.[1] They have set forth criteria that help to delineate patients with fibrositis from those with other similar pain syndromes; these criteria were amplified in my article. This, at least, is a start in the scientific study of this group of patients, for it enables investigators to compare results in similar patient populations. Such criteria should not be misconstrued as implying that fibrositis is a distinct disease entity; that distinction can only be made if reproducible pathology (psychological or organic) is discovered.

Weinberger's contention that no pathology has ever been found and that, therefore, the term fibrositis should be abandoned is hardly in accord with the spirit of scientific curiosity that leads to new insights. One need only look at the history of medicine to see the folly of such thinking. To wit, in polymyalgia rheumatica (PMR), a disease with many symptoms in common with fibrositis, there is only one major abnormal laboratory test finding: an elevated sedimentation rate. If we were not cognizant of this fact, should we also call PMR a "psychophysiologic state"? Indeed, the ubiquitous history of early morning stiffness and the exacerbation of the symptoms of fibrositis by changes in the atmospheric pressure are so reminiscent of many of the better defined rheumatic disorders that one has to be skeptical of any purely psychophysiologic explanation.

I suspect that if modern medical training paid more attention to "the common aches, pains, sorenesses . . . of humankind," rather than emphasizing the unusual and the esoteric, the burgeoning paramedical pseudosciences would have fewer devotees. Fibrositis, whatever it is, is just such a problem. Finally, I would remind Dr. Weinberger of some words of Claude Bernard: "It is what we think we know already that often prevents us from learning."

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Acetylcholine Replacement Therapy in the Management of Huntington's Disease

To the Editor: Evidence suggests that the choreiform manifestations of Huntington's disease (HD) are caused by deficient acetylcholine synthesis in striatal neurons.[1] This hypothesis was tested in the management of two cases of HD that we have followed for longer than a year. Transmitter replacement of central cholinergic synapses was achieved orally by the combined administration of an acetylcholine precursor (lecithin) and a cholinesterase inhibitor, pyridostigmine bromide (Mestinon). Pyridostigmine bromide was chosen,

rather than physostigmine, because it is less toxic than physostigmine and it is available in a convenient and palatable form.

The first patient was a 37-year-old white woman with established HD of seven years' duration (notable choreiform manifestations with persistent involuntary rotatory movements of the neck, irregular fidgeting of the hands, prancing gait with pronounced swaying of torsum when walking). This patient received 60 mg per day of pyridostigmine bromide given orally in concentrate form (Mestinon) and 12 grams per day of lecithin in capsules.

After four weeks of therapy a gradual reduction in range and amplitude of the choreiform movements became apparent. The patient was able to groom herself and walk unassisted. This improvement persisted as long as the pyridostigmine-lecithin therapy was continued. The deliberate interruption of this regimen, four months after initiation of therapy, induced the reemergence of the choreiform symptomatology in its unmodified form. Upon resumption of therapy, chorea gradually subsided and was brought under control within three weeks. This patient has been maintained on this regimen for 30 months without any ill effects or overt signs of toxicity or degeneration of other systems. She has been able to gain considerable weight (8 pounds), partly owing to the ability to feed herself more adequately.

A second patient, with strikingly similar clinical features, responded equally well to this therapeutic regimen. Within three weeks choreiform movements were reduced by 80 percent and the patient was able to feed himself and gained 14 pounds.

We have reason to believe, therefore, that acetylcholine replacement therapy can be achieved successfully by the oral administration of an appropriate acetylcholine precursor and a cholinesterase inhibitor. These pharmacological manipulations appear to be safe and quite effective in the management of choreiform components of HD. The response is rather slow in onset and is seldom evident before four to six weeks from the onset of therapy. These results are permanent and stable provided that this regimen is maintained.

In summary, it appears that transmitter replacement of central cholinergic synapses can be a practical routine and that it can be achieved with relative impunity by the simultaneous administration of an acetylcholine precursor and a cholinesterase inhibitor. In 1978 Barbeau[2] advocated the use of choline or lecithin as a possible means to replenish central cholinergic synapses. There are several neurological conditions for which there is presumptive evidence that some of the manifestations of the disease are the expression of a central cholinergic deficit. Huntington's chorea, Friedreich's ataxia, presenile dementia and Gilles de la Tourette's syndrome seem to fall into this category.

I believe that lecithin replacement, per se, is only weakly effective though assuredly safe. Its actions, however, can be enhanced by a moderate degree of inhibition of brain cholinesterase that can be achieved by the oral route with pyridostigmine bromide in doses ranging from 60 to 120 mg per day.

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Stewards of the Environment

To the Editor: The comments in the July editorial "There Will Be Changes Down the Road"[1] were intriguing. Although I generally agree that our government has spent money with abandon, the issues we face in health care, in our support of the elderly and in the continuation of medical research must be faced and appropriate alternative solutions sought.

I must, however, disagree with the statement that there is Biblical support for how mankind has reacted in his environment. Nowhere does there appear in that document commands or even suggestions to licentiously procreate or *exploit* our earth. To the contrary, if carefully studied, the Bible explicitly states that we humans are to be stewards of our environment; it indicates that God put us here to use the earth, not to abuse it. I am firmly convinced that the end of our world will occur when man has used up the earth and we perish in our own stupidity. I would hope that all physicians would in fact carefully use the Biblical guidelines which "make as much sense now as

Items submitted for the Correspondence section should be typed double-spaced (including references) with conventional margins. The text should not exceed 600 words.

ever." It is precisely because we are ignoring them that the earth is losing its battle against humanity.

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REFERENCE

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A Patient-as-Insurer Option

To the Editor: In a strict fee-for-service practice situation—that is, one in which the patient pays 100 percent of his medical expenses—a definable portion of the charge goes toward payment of the physician's malpractice insurance premiums. Perhaps the patient can eliminate part or all of the malpractice fee he ordinarily pays by acting as the insurer. In the event of a bad outcome, including one related to noncriminal negligence on the part of the physician, the patient, as insurer, would assume the burden of any liability. The availability of this option to the patient depends, of course, on a mechanism by which insurance companies reduce a physician's malpractice premiums in proportion to the fraction of his patients that choose to act as insurers.

The availability to the patient of such an option may have various advantages. The overall cost of medical care should diminish. In addition to the direct reduction in the proportion of the health care dollar paying for malpractice insurance, an even greater saving may be anticipated from the decreased pressure to practice defensive medicine. The physician would feel less need to order, for medical-legal reasons, an additional test to further substantiate a clinical judgment already corroborated by adequate objective data. The physician-patient relationship, and indeed other aspects of the quality of care, might improve with a reduction in the physician's concern that the patient he is trying to help represents a potential legal adversary. Those patients who tend to be less litigious—who choose to act as insurers—would reap the benefits of reduced medical expenditures. They need not subsidize those more prone to litigation.

Although for illustrative purposes a patient was chosen who pays 100 percent of his own medical expenses, the essential point of the patient-as-insurer option does not relate to payment for routine services, but rather to liability in case of a bad outcome. As such, it may apply as well to patients covered by private medical insurance. The reduced cost of medical care under this scheme—reflecting at least the easily quantified reduced malpractice insurance, and probably also the reduced defensive medicine expenditure—must be returned to the patient in the form of lower insurance premiums, or other benefits.

A by-product of this option is reinforcement of the understanding that even with its advances, modern medicine cannot guarantee outcomes. There are no absolutely safe therapies (who would have predicted the implication of tampons in toxic shock syndrome), only relative degrees of risk and ignorance.

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Immunologic Basis of Preeclampsia and Eclampsia

To the Editor: In the July Medical Staff Conference[1] a number of important features of preeclampsia and eclampsia were highlighted: there are impressive physiological abnormalities that rapidly return to normal with the termination of pregnancy; it is a multisystem disease; a common denominator is poor tissue perfusion; the hypertension and sodium retention are secondary rather than primary.

In light of the above features and recent findings by Jacob[2] regarding the role of endothelial cell damage by complement stimulated granulocyte-platelet aggregates, an immunologic basis of this disease appears more certain. Furthermore, this immune mechanism most likely operates by way of soluble immune complexes formed in slight antigen excess.

In preeclampsia, immune complexes have been found in kidneys,[3] liver[4] and placental bed.[5] They are known to occur in the placental bed with increased frequency in twin and molar pregnancy, conditions in which there is an increased likelihood of trophoblast invasion of the maternal circulation. That trophoblast is antigenic is well known and that it invades the maternal circulation has also been long known.

Similarly Hulka and co-workers[6] have shown antitrophoblastic antibodies to be present in increasing strength during labor and the immediate postpartum period in patients with preeclampsia. In an article by Scott[7] determination of ABO and HLA antigens and sex ratios of infants born to 46 women with preeclampsia-eclampsia in compari-

son with normal controls disclosed no predominant blood group, HLA haplotype or qualitative difference in maternal-fetal incompatibility. These results suggested that an immune link must be associated with fetoplacental tissue-specific antigen. Although preeclampsia is a disease of primigravidae, often those multigravidae in whom this syndrome develops are pregnant from different fathers[8] and, therefore, I believe that it is the 50 percent of trophoblast contributed to by the father and its subsequent immunogenicity that sets the stage for this disease, rather than maternal immunological defects per se.

Typically one of three situations arises in a primigravida encountering antigen for the first time: The maternal antibody response may be poor in which case there is large antigen excess and no pathological immune complexes are formed. Second, those mothers in whom large antibody excess quickly develops become free of disease. However, third, in those mothers with an intermediate response, immune complexes are liable to be formed with slight antigen excess complexes that are extremely toxic and that will activate complement and aggregate leukocytes and platelets (apparently secondary to adhesion of the Fc fragment of antibodies to a specific platelet receptor) and damage endothelium producing a multisystem vasculitis.

In the past complement levels have been found to be no different between preeclamptic patients and normal.[9] However, this is a very crude test because to see a decrease in complement levels one would have to be activating complement at a rate that exceeded the ability to replace complement by increased synthesis or release. A more sensitive test is to look for byproducts of complement activation—C3a and C5a. Recent reports by Jacob[2,10] correlate the clinical severity of lupus with the degree of granulocyte aggregation and C5a levels in the circulation of patients. Current work (unpublished) is attempting to correlate the levels of C5a with the severity of preeclampsia-eclampsia. A number of interesting aspects are suggested by these findings: (1) The immunogenetic role of the father. (2) That superoxide dismutase and high doses of steroids (30 mg per kg of body weight of methylprednisolone)—drugs known to inhibit complement-induced leukoaggregation—may have a role in preeclampsia-eclampsia. (3) That abruptioplacentae may represent an exaggerated form of vasculitis, with increased tissue necrosis and consequent release of large amounts of thromboplastin and other antigenic material leading to a severe hemorrhagic diathesis usually not seen in the preeclampsia-eclampsia syndrome.

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Diagnosing Preeclampsia in Late Pregnancy

To the Editor: The Medical Staff Conference on preeclampsia and eclampsia[1] in the July issue was excellent. I felt it was a well-organized, well-presented, concise statement of the current knowledge.

I have been commonly faced with a situation not addressed in the article: A primigravida with normal blood pressure, no proteinuria and no edema evident on prenatal examinations enters the hospital in labor at term with a blood pressure of 140/90 mm of mercury, trace or 1+ proteinuria, minimal or no edema and hyperactive reflexes. The hypertension and hyperreflexia persist through labor. Is this patient preeclamptic? Does she need magnesium sulfate? If so, what dosage schedule?

DAVID G. STANGLAND, MD
Tonasket, Washington

REFERENCE

1. Roberts JM: Preeclampsia and eclampsia—Medical Staff Conference, University of California, San Francisco. West J Med 135:34-43, Jul 1981

* * *

Dr. Roberts Responds

To the Editor: The problem presented by Dr. Stangland is one that troubles a number of persons involved in the care of women during labor. This probably is one of the more striking examples

of the difficulty of diagnosing preeclampsia as opposed to other causes for blood pressure change in late pregnancy or in response to stress. It also presents the quandary of realizing that one is overdiagnosing a condition and weighing the risks of overdiagnosing versus missing a patient who truly has preeclampsia.

A number of authors have shown that blood pressure in patients is customarily higher in labor than during any other time during their pregnancy. This undoubtedly relates to the stress of labor and possibly to cardiovascular changes associated with uterine contractions independent of stress. However, it is also known that the most likely time for preeclampsia to accelerate, become more severe and possibly even proceed to eclampsia is during labor.

My approach has been to accept the fact that I am going to overdiagnose preeclampsia and to make the diagnosis of preeclampsia on the basis of blood pressure changes sufficient to arrive at the diagnosis of this condition. That is, an increase of 30 systolic or 15 diastolic from early pregnancy. The presence of proteinuria in the absence of ruptured membranes (which will contaminate urine and lead to a misdiagnosis of proteinuria) is even stronger evidence of preeclampsia. I accept the fact that I overdiagnose preeclampsia since the interventions that I plan on the basis of this overdiagnosis have been shown, with extensive experience, to have a very beneficial risk-to-benefit ratio. Interventions I choose are to administer magnesium sulfate intravenously in the manner that has been presented by Zuspan[1] and to be certain that the fetus, which in a preeclamptic woman is at increased risk, is monitored electronically during labor. I stress the fact that this is my opinion, there are a number of physicians, especially in Europe, who virtually never use anticonvulsants. I would say, though, in the experience I have had at the University of California and other places over the last ten years, the only patients that I have seen convulse have been women who have minimal findings of preeclampsia when they entered labor and therefore were not treated with prophylactic anticonvulsant therapy with magnesium sulfate.

Magnesium sulfate, when used appropriately as pointed out in the Medical Staff Conference, is a safe drug for the mother and perhaps even more important, compared with all other anticonvulsant therapy, is extremely safe for the fetus. Dosage schedule for magnesium sulfate is 4 grams administered intravenously over about five minutes. This is followed by 1 gram intravenously per hour. The continuation of the magnesium at this rate is determined by the patient's urinary output. Since magnesium is excreted solely in the urine, urinary output of 40 ml an hour is necessary to continue treatment at this empiric dosage. To further check on magnesium levels the patient's deep tendon reflexes are followed; if deep tendon reflexes disappear, magnesium should be discontinued. For a patient who is diuresing rapidly during magnesium therapy, it may be necessary to give higher doses of magesium than 1 gram an hour. This, however, should be carried out with great care, following deep tendon reflexes every 15 minutes and also following serum magnesium levels at approximately two hour intervals for the duration of the administration. With this approach, magnesium sulfate is a safe and efficacious drug in the prevention of intrapartum and postpartum eclampsia.

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REFERENCE

1. Zuspan FP: Treatment of severe preeclampsia and eclampsia. Clin Obstet Gynecol 9:945, 1966

BOOK REVIEWS

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

ARCHIVES OF FAMILY PRACTICE—Volume I, 1980—Edited by John P. Geyman, MD, Professor and Chairman, Department of Family Medicine, University of Washington School of Medicine. Appleton-Century-Crofts, 292 Madison Avenue, New York City (10017), 1980. 413 pages, $34.50.

With the publication of *Archives of Family Practice—1980,* John P. Geyman, MD has established himself as the leading editor and compiler of the family practice movement. Since 1974 Dr. Geyman has not only been the editor of *The Journal of Family Practice* but he has also found time to write or edit three previous volumes. The current publication now purports to be the first of an annual series.

Archives of Family Practice—1980 will be of special interest to students, educators, and historians of family practice, but it also affords interesting browsing for the family physician who has an intellectual curiosity regarding the development and changes of his specialty. The current volume encompasses three major subject areas: "Evolution of the Specialty," "Undergraduate Education in Family Practice" and "Clinical Research in Family Practice." Each section contains some 12 to 14 papers published in their entirety and some 20 to 25 papers published in abstract form. Many, but not all, of the papers are preceded by a summary paragraph. In the preface the editor states that "where appropriate" authors have been asked to update their papers with current comments but in the text no indication of possible changes or comments is made. Editorial comment or critique of the papers is also lacking. Such added comments would increase the reader's enjoyment.

The abstracts, credit for some of which the editor attributes to his son, are well done and do present a concise documentation of the essential points made by the article reviewed. They are very readable and informative.

This reviewer found the section "Clinical Research in Family Practice" to be of unusual interest. Papers presented a potpourri of practice problems as seen in the office which emphasizes continuing ambulatory patient care. Statistical analyses are given of presenting complaints, physician-patient interaction and outcome of therapy. Though some of the data presented and conclusions drawn are open to critical review and possibly varying interpretation, the mass and variety of data assembled are impressive. Many areas are opened for further study.

Though *Archives of Family Practice—1980* presents no strictly original material it is an impressive collection, under one cover, of the considerable literature relating to the development and maturation of the changing specialty of family practice. It and subsequent volumes of the series will be of interest to many readers.

HERBERT A. HOLDEN, MD
San Leandro, California
Former President, American Academy of Family Physicians (1975)

* * *

ANNUAL REVIEW OF NEUROSCIENCE—Volume 4, 1981—Editor: W. Maxwell Cowan, Washington University School of Medicine; Associate Editors: Zach W. Hall, University of California, San Francisco, and Eric R. Kandel, College of Physicians and Surgeons of Columbia University. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1981. 556 pages. $20.00 (USA). $21.00 (elsewhere).

This volume is the fourth in the neuroscience series published by Annual Reviews. As was true in previous editions, this volume offers comprehensive reviews which are of interest to practicing physicians, basic neuroscientists and students of the philosophy of science.

For practicing physicians, Elliott Weitzman provides a review of sleep disorders. This chapter alone is worth the price of the volume. It is detailed and extensively referenced and includes guidelines for treatment. Daniel Drachman contributes a chapter on the biology of myasthenia gravis. This section covers the clinical features, pharmacology, cell biology, immunology and therapy of myasthenia gravis. It is the most up-to-date current review of the topic.

For the basic neurobiologist, there are chapters on the enteric nervous system, cytoskeletal elements in neurons and synaptic plasticity. Excellent reviews of the physiology of the calcium channel, the vestibulo-ocular reflex and the use of systems analysis in the study of eye movements are also included. The cellular physiology of β-adrenergic receptor subtypes is extensively reviewed. Neuroembryologists will find interest in the chapters on the development of the neuromuscular junction and on motor neuron sprouting.

For students of the philosophy of science, Roger Sperry provides a provocative introductory essay on the role of science in society. He persuasively argues that science is the best, perhaps only, instrument by which to alleviate the problems which attend modern technological society. The justifications for this view are grounded in the neurobiological concepts of consciousness. Those who seek direction for future scientific endeavor are encouraged to read Sperry's article.

In summary, this volume has appeal to a variety of disciplines and is highly recommended.

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Chief Resident
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in memoriam

California Medical Association

ARMITSTEAD, REO B., Carpinteria. Died November 13, 1980, age 81. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr. Armitstead was a retired member of the Ventura County Medical Society.

BARNARD, JAMES F., Bakersfield. Died July 24, 1981, in an automobile accident near Los Banos, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1936. Licensed in California in 1936. Dr. Barnard was a retired member of the Kern County Medical Society.

CARLIN, FAYETTE ALLEN, JR., Chula Vista. Died July 18, 1981, in Chula Vista, aged 48. Graduate of the University of California Irvine, California College of Medicine, 1962. Licensed in California in 1963. Dr. Carlin was a member of the San Diego County Medical Society.

CARROLL, DAVID VINCENT, Tiburon. Died August 10, 1981, in San Francisco, aged 36. Graduate of the National University of Ireland, University College of Dublin, 1969. Dr. Carroll was a member of the San Francisco Medical Society.

CHALMERS, JAMES FERGUSON, La Jolla. Died August 21, 1981, in La Jolla, aged 93. Graduate of the University of Edinburgh Faculty of Medicine, Edinburgh, 1912. Licensed in California in 1931. Dr. Chalmers was a retired member of the San Diego Medical Society.

DUNN, ROBERT D., Palo Alto. Died August 16, 1981, in Santa Rosa of injuries received in horseback riding accident, aged 77. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Dunn was a retired member of the Santa Clara County Medical Society.

GILLICK, F. GEORGE, San Jose. Died August 6, 1981, in San Jose, aged 70. Graduate of St. Louis University School of Medicine, 1935. Licensed in California in 1945. Dr. Gillick was an associate member of the Santa Clara County Medical Society.

HOLKO, JOHN EUGENE, San Francisco. Died August 12, 1981, in Walnut Creek, aged 70. Graduate of the University of Michigan Medical School, Ann Arbor, 1936. Licensed in California in 1937. Dr. Holko was a retired member of the San Francisco Medical Society.

ORR, DOROTHY R. (DOROTHY R. ORR GOFF), San Francisco. Died July 8, 1981, in San Francisco, aged 68. Graduate of the University of Michigan Medical School, Ann Arbor, 1939. Licensed in California in 1942. Dr. Orr was a retired member of the San Francisco Medical Society.

STOREY, ALFRED D., Palo Alto. Died August 7, 1981, in Palo Alto, aged 76. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1937. Licensed in California in 1937. Dr. Storey was a retired member of the Santa Clara County Medical Society.

WARREN, STAFFORD L., Los Angeles. Died July 26, 1981, in Pacific Palisades of myocardial infarction, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Warren was a member of the Los Angeles County Medical Association.

New Mexico Medical Society

FOX, FREDERICK G., Albuquerque. Died August 9, 1981, in Albuquerque, aged 92. Graduate of the Chicago College of Medicine and Surgery, 1914. Licensed in New Mexico in 1946. Dr. Fox was a retired member of the Albuquerque & Bernalillo County Medical Association.

SENESCU, ROBERT ALAN, Albuquerque. Died August 10, 1981, in Albuquerque, aged 60. Graduate of Boston University School of Medicine, 1948. Licensed in New Mexico in 1967. Dr. Senescu was a member of the Albuquerque & Bernalillo County Medical Association.

ZEIGLER, JOEL, Clovis. Died July 21, 1981, aged 81. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1934. Licensed in New Mexico in 1946. Dr. Zeigler was a retired member of the De Baca-Curry-Roosevelt County Medical Association.

Washington State Medical Association

BELLAS, NORMAN M., Wenatchee. Died June 6, 1981, in Wenatchee, aged 84. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1926. Licensed in Washington in 1930. Dr. Bellas was a retired member of the Chelan Douglas County Medical Society and the the American Medical Association.

BROXON, WILLIAM D., Seattle. Died July 2, 1981, in Seattle of myocardial infarction, aged 54. Graduate of the University of Colorado School of Medicine, Denver, 1953. Licensed in Washington in 1959. Dr. Broxon was a member of the King County Medical Society.

HOLMES, ELIZABETH J., Seattle. Died July 7, 1981, in Seattle, aged 53. Graduate of the Medical College of Pennsylvania, Philadelphia, 1954. Licensed in Washington in 1959. Dr. Holmes was a member of the King County Medical Association.

SCOTT, JAMES MELVIN, Everett. Died July 5, 1981, in Darrington of myocardial infarction, aged 46. Graduate of the University of Oregon Medical School, Portland, 1961. Licensed in Washington in 1969. Dr. Scott was a member of the Snohomish County Medical Society.

Announcing a new measure of relief of symptoms of seasonal and perennial rhinitis

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Beconase® Nasal Inhale

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relief that goes the distance

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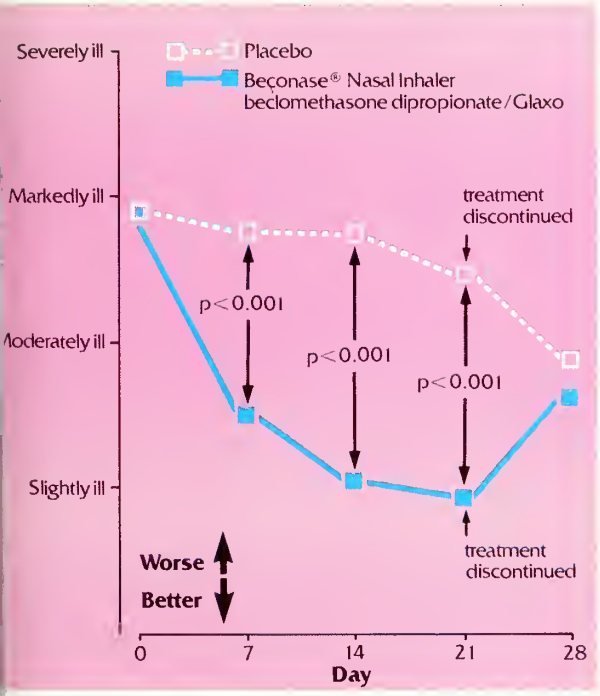
To relieve the symptoms of hay fever and nasal allergies, each microdose administration (42 mcg) of Beconase® Nasal Inhaler delivers active ingredient to the nasal mucosa. And at recommended doses (one inhalation per nos 2-4 times daily), does not cause side effects commonly associated with antihistamines ar decongestants.

ovides continuous relief of nasal ngestion, sneezing, runny nose d itching associated with hay ver and nasal allergies

nificantly greater improvement than placebo nsistently demonstrated in clinical trials[1]

gnificantly superior to placebo in nical trial[2]



nges in clinical condition in 51 seasonal gic rhinitis patients originally presenting n symptoms of marked severity. In addition verall improvement in clinical condition, e was a statistically significant improvement 14, and 21 days in nasal obstruction, runny e, sneezing and itching of the nose.

Pierre et al., Data on File)

Delivered directly to the nasal mucosa

- symptom improvement is usually apparent within a few days (in some patients, it may take up to two weeks)[2]
- full 24-hour relief within one to two weeks with regular use[1]
- clinical studies have shown no evidence of adrenal insufficiency

Avoids the problems of antihistamines and decongestants

- no drowsiness
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No histopathologic changes in nasal mucosa were shown in patients treated up to one year

Occasional side effects—primarily infrequent (about 10%) and clinically insignificant nasal irritation, burning and sneezing*

Preferred by 70% of patients in four studies[3 6]

Rare instances of localized candida infections, bloody nasal discharge and nasal ulceration have been reported

Please see last page for prescribing information.

A major therapeutic advance in seasonal and perennial rhinitis symptom reli

NEW

Beconase® Nasal Inhale

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DESCRIPTION Beclomethasone dipropionate, USP, the active component of BECONASE Nasal Inhaler, is an anti-inflammatory steroid having the chemical name, 9-Chloro-11β, 17, 21-trihydroxy-16β-methylpregna-1, 4-diene-3, 20-dione 17,21-dipropionate

Beclomethasone dipropionate is a white to creamy-white, odorless powder with a molecular weight of 521.25 It is very slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and in alcohol

BECONASE Nasal Inhaler is a metered-dose aerosol unit containing a microcrystalline suspension of beclomethasone dipropionate-trichloromonofluoromethane clathrate in a mixture of propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid Each canister contains beclomethasone dipropionate-trichloromonofluoromethane clathrate having a molecular proportion of beclomethasone dipropionate to trichloromonofluoromethane between 3:1 and 3:2 Each actuation delivers from the nasal adapter a quantity of clathrate equivalent to 42 mcg of beclomethasone dipropionate, USP The contents of one canister provide at least 200 metered doses

CLINICAL PHARMACOLOGY Beclomethasone 17,21-dipropionate is a diester of beclomethasone, a synthetic corticosteroid which is chemically related to dexamethasone Beclomethasone differs from dexamethasone only in having a chlorine at the 9-alpha position in place of a fluorine Animal studies showed that beclomethasone dipropionate has potent glucocorticoid and weak mineralocorticoid activity

The mechanisms for the anti-inflammatory action of beclomethasone dipropionate are unknown The precise mechanism of the aerosolized drug's action in the nose is also unknown Biopsies of nasal mucosa obtained during clinical studies showed no histopathologic changes when beclomethasone dipropionate was administered intranasally

The effects of beclomethasone dipropionate on hypothalamic-pituitary-adrenal (HPA) function have been evaluated in adult volunteers by other routes of administration Studies are currently being undertaken with beclomethasone dipropionate by the intranasal route, which may demonstrate that there is more or that there is less absorption by this route of administration There was no suppression of early morning plasma cortisol concentrations when beclomethasone dipropionate was administered in a dose of 1000 mcg/day for one month as an oral aerosol or for three days by intramuscular injection However, partial suppression of plasma cortisol concentration was observed when beclomethasone dipropionate was administered in doses of 2000 mcg/day either by oral aerosol or intramuscularly Immediate suppression of plasma cortisol concentrations was observed after single doses of 4000 mcg of beclomethasone dipropionate Suppression of HPA function (reduction of early morning plasma cortisol levels) has been reported in adult patients who received 1600 mcg daily doses of oral beclomethasone dipropionate for one month In clinical studies using beclomethasone dipropionate intranasally, there was no evidence of adrenal insufficiency

Beclomethasone dipropionate is sparingly soluble When given by nasal inhalation in the form of an aerosolized suspension, the drug is deposited primarily in the nasal passages A portion of the drug is swallowed Absorption occurs rapidly from all respiratory and gastrointestinal tissues There is no evidence of tissue storage of beclomethasone dipropionate or its metabolites *In vitro* studies, have shown that tissue other than the liver (lung slices) can rapidly metabolize beclomethasone dipropionate to beclomethasone 17-monopropionate and more slowly to free beclomethasone (which has very weak anti-inflammatory activity) However, irrespective of the route of entry the principal route of excretion of the drug and its metabolites is the feces In humans, 12% to 15% of an orally administered dose of beclomethasone dipropionate is excreted in the urine as both conjugated and free metabolites of the drug The half-life of beclomethasone dipropionate in humans is approximately 15 hours

Studies have shown that the degree of binding to plasma proteins is 87%.

INDICATIONS AND USAGE BECONASE Nasal Inhaler is indicated for the relief of the symptoms of seasonal or perennial rhinitis in those cases poorly responsive to conventional treatment

Clinical studies have shown that improvement is usually apparent within a few days However, symptomatic relief may not occur in some patients for as long as 2 weeks Although systemic effects are minimal at recommended doses, BECONASE should not be continued beyond 3 weeks in the absence of significant symptomatic improvement BECONASE should not be used in the presence of untreated localized infection involving the nasal mucosa

CONTRAINDICATIONS Hypersensitivity to any of the ingredients of this preparation contraindicates its use

WARNINGS The replacement of a systemic corticosteroid with BECONASE Nasal Inhaler can be accompanied by signs of adrenal insufficiency

When transfered to BECONASE Nasal Inhaler, careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids This is particularly important in those patients who have associated asthma or other clinical conditions, where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increase the likelihood of HPA suppression compared to a therapeutic dose of either one alone Therefore, BECONASE treatment should be used with caution in patients already on alternate day prednisone regimens for any disease

PRECAUTIONS General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely When such an infection develops, it may require treatment with appropriate local therapy or discontinuance of treatment with BECONASE Nasal Inhaler

Beclomethasone dipropionate is absorbed into the circulation Use of excessive doses of BECONASE Nasal Inhaler may suppress HPA function

BECONASE should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections or ocular herpes simplex

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred

Although, systemic effects have been minimal with recommended doses, this potential increases with excessive doses Therefore, larger than recommended doses should be avoided

Information for Patients: Patients should use BECONASE Nasal Inhaler at regular intervals since its effectiveness depends on its regular use The patient should take the medication as directed It is not acutely effective and the prescribed dosage should not be increased Instead nasal vasoconstrictors or oral antihistamines may be needed until the effects of BECONASE Nasal Inhaler are fully manifested One to two weeks may pass before full relief is obtained The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient's Instructions carefully

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 we inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have n performed

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by route No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate inhalation route

Pregnancy Category C: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the ra beclomethasone dipropionate was administered by inhalation at 10 times the human dose or orally at 1000 times the dose There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids durin nancy Such infants should be carefully observed

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk Because oth costeroids are excreted in human milk, caution should be exercised when BECONASE Nasal Inhaler is administ nursing women

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established

ADVERSE REACTIONS In general, side effects in clinical studies have been primarily associated with the nasal membranes

Adverse reactions reported in controlled clinical trials and long term open studies in patients treated with BECON described below

Sensations of irritation and burning in the nose (11 per 100 patients) following the use of BECONASE Nasal Inhaler ha reported. Also, occasional sneezing attacks (10 per 100 patients) have occurred immediately following the use of tranasal inhaler

Localized infections of the nose and pharynx with *Candida albicans* have occurred rarely (See PRECAUTIONS).

Less than 2 per 100 patients reported transient episodes of bloody discharge from the nose

Ulceration of the nasal mucosa has been reported rarely Systemic corticosteroid side effects were not reported du controlled clinical trials If recommended doses are exceeded, however, or if individuals are particularly sensitive, sy of hypercorticism, i.e., Cushing's syndrome, could occur

DOSAGE AND ADMINISTRATION *Adults and Children 12 years of age and over* the usual dosage is one inhalation (42 each nostril two to four times a day (total dose 168-336 mcg/day) Patients can often be maintained on a maximum one inhalation in each nostril three times a day (252 mcg/day).

In patients who respond to BECONASE Nasal Inhaler, an improvement of the symptoms of seasonal or perennial usually becomes apparent within a few days after the start of BECONASE Inhaler therapy

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OVERDOSAGE When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal s sion may appear If such symptoms appear, the dosage should be decreased The oral LD_{50} of methasone dipropionate is greater than 1 g/kg One canister of BECONASE contains 8 4 mg of beclomethasone dipro therefore acute overdosage is unlikely

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References

1. Data on file at Glaxo Inc.
2. St Pierre J, Langlois C and Elie R Data on file
3. Mygind N *Brit Med J* 4 464, 1973
4. Wheatley D *Curr Ther Res* 19 612, 1976
5. Vilsvik J et al *Clin Allergy* 5 291, 1975
6. Lofkvist T and Svensson G *Acta Allergol* 30 227, 1975

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(Continued from Page 27)

SITUATIONS WANTED

GASTROENTEROLOGIST/INTERNIST: 32-year-old ABM certified, GI eligible skilled in all endoscopic procedures with excellent references desires academic-oriented private practice opportunity for July 1982. Box 6239, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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INTERNIST-ENDOCRINOLOGIST, 31, ABIM, university trained with interest in diabetes, nutrition and obesity. Seeks private practice opportunity in Western States. Available June 1982. Reply Box 6246, Western Journal of Medicine, 731 Market St., San Francisco 94103.

NEUROLOGIST, board eligible, university trained with competence in EMG-NCS, EEG and CT. Seeks private practice opportunity in Western States. Available July 1982. Reply Box 6247, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 38)

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INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract

CONTRAINDICATIONS

None known

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50 The physican should be cognizant of this possibility in prescribing RIMSO® - 50. If anaphylactoid symptoms develop, appropriate therapy should be instituted

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications

Pregnancy Category C Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2 5-12 gm/kg) Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters Topical doses (5 gm/kg first two days, then 2 5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1 1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration Usually this becomes less prominent with repeated administration

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm The medication is expelled by spontaneous voiding It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained Thereafter, time intervals between therapy may be increased appropriately

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia (Saddle block has been suggested).

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Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution)
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(Continued from Page 23)

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Asthma: Impact and Strategies for Change.** UCLA. Saturday-Sunday. 14 hrs. $85.

March 3-6—**Third World Congress for Bronchology.** World Assn. for Bronchology and American College of Chest Physicians at Town and Country, San Diego. Wednesday-Saturday. $250, WAB and ACCP members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 3-6—**Immunology and the Clinical Practice of Allergy—6th Annual Course.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs.

March 5—**Diabetes.** UCD at Red Lion Inn, Sacramento. Friday.

March 6—**Cardiology for the Primary Care Physician II: Office Diagnosis of the Cardiac Patient.** PMC. Saturday. 6 hrs. $95.

March 7-10—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday.

March 10—**Hypothyroidism—Unmasked.** LLU. Wednesday. 4 hrs. $30.

March 11-13—**Therapeutic and Diagnostic Uses of the Cardiac Catheter.** Am. College of Cardiology at Bonaventure Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 12-13—**Stress Testing Today and Tomorrow.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

March 12-14—**Western Institute on Epilepsy.** UCLA at Marriott, Los Angeles. Friday-Sunday. $60.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

March 19-20—**Non-Invasive Cardiology Conference.** Clairemont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 22-April 2—**30th Annual Review of Internal Medicine.** USC., 12 days.

April-June—**Allergy/Immunology for the Practicing Internist.** UCLA. Wednesday evenings.

April 1-4—**Principles in the Practice of Allergic Diseases in Adults and Children.** UCD at Del Monte Hyatt, Monterey. Thursday-Sunday.

April 3—**Clinics in Medicine—Cardiology.** PMC. Saturday. 3 hrs. $40.

April 14—**Cardiology Update 1982.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

April 23-30—**Dermatology.** UCD. One week.

OBSTETRICS AND GYNECOLOGY

December 7-9—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Rancho Las Palmas Resort, Rancho Mirage. Monday-Wednesday. Contact: MHMC-UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 14-16—**What's New in Perinatal-Neonatal Care.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Wednesday. 16 hrs. $185.

January 9-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $395.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

February 6-7—**Los Angeles OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 8-12—**37th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 14-17—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 20-24—**American Fertility Society.** See Of Interest To All, March 20-24.

March 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

PEDIATRICS

December 12—**Managing Pediatric Emergencies.** No. Calif. Chapter, Am. Academy of Pediatrics, at Union Square Holiday Inn, San Francisco. Saturday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

December 14-16—**What's New in Perinatal-Neonatal Care.** See Obstetrics and Gynecology, December 14-16.

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

January 31-February 2—**7th Annual Winter Ski and Study Symposium.** Calif. Chap. 2, American Academy of Pediatrics, at Mammoth Mountain. Sunday-Wednesday. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

March 12-14—**Combined Southern California Pediatric Postgraduate Program.** Calif. Chap. 2, American Academy of Pediatrics, at Palm Springs. Friday-Sunday. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

April 2-3—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 10-17—**Pediatric Emergencies.** See Emergency Medicine, April 10-17.

April 14—**Antibiotic Use in Pediatric Specialty Practice.** LLU. Wednesday. 4 hrs. $30.

April 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

PSYCHIATRY

January 21-26—**Psychiatric Symposium.** Continuing Medical Education, Inc., and Western Medical Center at Maui Surf Resort, Maui. Thursday-Tuesday. 24 hrs. Contact: CME, Inc., 2030 E. 4th St., #113, Santa Ana 92705. (714) 547-5186.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

January 31-February 4—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 13-14—**Emotions in Health and Illness: Foundations of Clinical Practice.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. 12 hrs.

February 19-20—**Heinz Von Foerster on Cybernetics, Language and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

March 12-14—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Friday-Sunday. 24 hrs. $275.

March 27—**Reconsiderations of Psychoanalytic Listening.** Southern California Psychoanalytic Society at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs. Carol Ziff, Exec. Sec., So. Calif. Psychoanalytic Soc., 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

RADIOLOGY AND PATHOLOGY

January 31-February 5—**4th Annual Winter Conference in the High Sierra—OB/GYN Imaging.** American College of Medical Imaging at Sahara, Lake Tahoe. Sunday-Friday. 25 hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 3-5—**New Directions in Clinical Laboratory Assays: 4th Immunology Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 18 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 10—**Pulmonary Function Tests and Blood Gas Interpretation.** LLU. Wednesday. 4 hrs. $30.

March 3-5—**Sierra Radiology Conference—3rd Annual.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at North Lake Tahoe. Wednesday-Friday. 18 hrs. $265. Contact: Michael H. Reid, PhD, MD, Sac. Rad. Research and Ed. Fndn., P.O. Box 161112, Sacramento 95816.

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section. UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

November 17-20—**U.S. Section of International College of Surgeons.** Hotel del Coronado, Coronado. Tuesday-Friday. Contact: George Evashwick, MD, 204 Roswell Ave, Long Beach 90803.

November 19-20—**Critical Decisions in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Friday. 12 hrs. $200. Contact: Lore Kahane, Cedars-Sinai Med. Ctr., Rm. 2049, P.O. Box 38750, Los Angeles 90048. (213) 855-5547.

December 2-4—**Invasion of the Cornea and Lens.** UCSF. Wednesday-Friday.

December 2-5—**Society for Office Based Surgery—3rd Annual Meeting.** Jointly sponsored by Sharp Memorial Hospital at Vacation Village Hotel, San Diego. Wednesday-Saturday. $75, members; $125, nonmembers. Contact: Purvis L. Martin, MD, Soc. of Office Based Surgery, P.O. Box 9494, San Diego 92109.

December 3-6—**Bone Grafting: Biology and Application.** Plastic Surgery Research Foundation at Hyatt Islandia, San Diego. Thursday-Sunday. 17 hrs. $275. Contact: Jack C. Fisher, MD, P.O. Box 33387, San Diego 92103.

December 4-5—**Management of Today's Endocrine Problems: A Medical and Surgical Update.** See Medicine, December 4-5.

December 5—**The Management of Thyroid Eye Disease.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

December 9-11—**Arthroscopic Surgery 1981.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. Contact: MHMC-UCI Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2311.

December 10-13—**Intensive Care for Neurological Trauma and Disease: Update 1981.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Mission Bay Hilton, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Comprehensive CNS Injury Fndn., P.O. Box 9494, San Diego 92109.

December 11-12—**Ophthalmology Update.** UCD, PMC, UCSF, STAN at Sheraton-Palace, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2761.

January 14-16—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Canyon Hotel, Palm Springs. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

January 15-16—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

January 30-February 6—**Office Urology for Urologists.** Univ. of Washington School of Medicine at Hyatt Regency, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 5-7—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Century Plaza, Los Angeles. Friday-Sunday. Contact: Drs. Richard Fleming and Toby Mayer, 9730 Wilshire Blvd., Suite 216, Beverly Hills 90212.

February 10-12—**Traumatic and Congenital Hand Surgery.** UCLA. Wednesday-Friday.

February 13-20—**Plastic Surgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 18-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass: II.** Cardiothoracic Research and Education Fndn. and Vascular Disease Fndn. at Hilton on Mission Bay, San Diego. Thursday-Sunday. Contact: CREF, P.O. Box 33185, San Diego 92103.

(Continued on Page 42)

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RAINDICATIONS: Not for use in the eyes or in the external ear canal eardrum is perforated. This product is contraindicated in those individuals ve shown hypersensitivity to any of its components.

ING: Because of the potential hazard of nephrotoxicity and ototoxicity due nycin, care should be exercised when using this product in treating extensive trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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(Continued from Page 40)

February 28-March 4—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

March 1-5—**Surgical Forum.** Society of Graduate Surgeons at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 4-5—**13th Annual Lecture and Postgraduate Seminar—Pediatric Ophthalmology and Strabismus Update.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

March 12—**Male Infertility Seminar.** Western Section, American Urological Assn., at Marriott, Los Angeles. Friday. Contact: Kathy De Santis, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

March 25-27—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

March 28-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Sunday-Wednesday.

March 31-April 4—**10th Annual Symposium on Vascular Surgery.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday. $385.

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

OF INTEREST TO ALL PHYSICIANS

November 15—**Dilemmas With Drugs in Clinical Practice.** Granada Hills Community Hospital and UCLA at Sheraton-Universal Hotel, North Hollywood. Sunday. Contact: Germaine Thrasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344.

November 16-20—**Postgraduate Institute for Primary Care Physicians—Symposium on Inpatient Care.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

December 4—**Nutritional Support: The Challenge for the Seriously Ill Patient.** Daniel Freeman Memorial Hospital and Marina Mercy Hospital at Daniel Freeman Mem. Hosp., Inglewood. Friday. 7 hrs. $60. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Mem. Hosp., 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 3427.

December 4-6—**Renal Problems, Fluid and Electrolyte Disorders in Office Practice—An Update for the Primary Care Physician.** Cypress Foundation at Hyatt Del Monte, Monterey. Friday-Sunday. 14 hrs. Contact: Cypress Fndn., P.O. Box 308, Salinas 93902. (408) 455-1833.

December 4-6—**Sports Medicine Conference—Athletes and Health.** UCSF at El Rancho Racquet Resort, Sacramento. Friday-Sunday. 17 hrs. $125.

December 4-11—**Behavioral Medicine and Primary Care in the 80's.** Professional Institutes and Univ. of So. Carolina School of Medicine at Ilikai Hotel, Honolulu. One week. 16 hrs. $300. Contact: Jeri McClain, USC School of Medicine, Office for Academic Affairs, Columbia, SC 29208. (803) 777-7470.

January 16—**Herpes Simplex: Clinical Practice and Research.** UCSF Cont. Ed. in Health Sciences at Fort Mason Conference Center, San Francisco. Saturday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 3-5—**Neurology for Non-Neurologists.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 6-7—**Immunology for the Family Physician.** UCLA. Saturday-Sunday.

February 7-12—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Friday.

February 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

February 13-14—**Emotions in Health and Illness.** See Psychiatry, February 13-14.

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 18-19—**Hospital Epidemiology for Physicians and Infection Control Teams.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. Contact: Richard P. Henke, MD, Memorial Hosp., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2431, ext. 23.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

March 1-2—**Treatment Issues in Geriatrics.** Western Gerontological Society and Washington State Psychiatric Assn. at Town and Country Hotel, San Diego. Monday-Tuesday. Contact: Barbara Freda, WGS, 785 Market St., Suite 1114, San Francisco 94103. (415) 543-2617.

March 8-12—**Sports Medicine.** Northwestern Univ. Center for Sports Medicine at Maui. Monday-Friday. 25 hrs. Contact: Bates Noble, MD, Northwestern Univ. Ctr. for Sports Medicine, 303 E. Chicago Ave., Chicago 60611.

March 10—**Pain Management.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

March 10-13—**Optimal Health: A Guide for Practicing Physicians.** Scripps Clinic and Research Fndn. at La Costa Resort Hotel, Carlsbad. Wednesday-Saturday. 22 hrs. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

March 12-17—**California Medical Association—111th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

March 15-19—**Sports Medicine.** Ohio State Univ. and Univ. of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19—**Diabetes and Nutrition Update.** UC and STAN at Hilton, San Francisco. Friday. Contact: UCD.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 20-24—**American Fertility Society—38th Annual Meeting and 15th Postgraduate Program.** MGM Grand, Las Vegas. Saturday-Wednesday. Contact: Herbert H. Thomas, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, AL 35256. (205) 933-7222.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 3-10—**Topics in Family Practice.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-17—**Management of Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

Needs Identification and Fulfillment Tailored to the Individual (NIFTI). UCSF. A new contemporary approach to formal continuing medical education. Participating physicians identify their own CME needs which will be met by a program specifically tailored by UCSF faculty for each individual physician. 25 hrs. minimum; 100, maximum. Fee: $350; $200, UCSF alumni. Contact: Extended Programs in Medical Education, 569-U, Univ. of Calif., San Francisco 94143. (415) 666-4251.

Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

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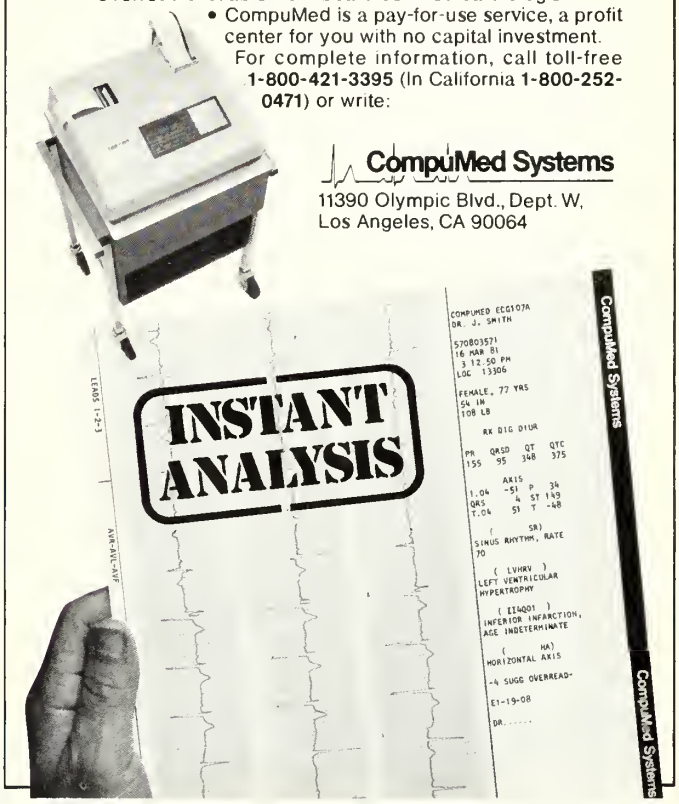

ALASKA

No courses announced.

IDAHO

See Washington Listings, February 13, March 6-13, and June 19-26.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category I credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

April 15-17—See Washington Listings.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American

Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 13-14—**Interim Meeting, New Mexico Medical Society.** Las Cruces. Friday-Saturday. Holiday Inn de Las Cruces. Scientific Program: **Oncology for the Eighties.** 7 credit hours, also AAFP Prescribed. Contact: New Mexico Medical Society, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

November 17-21—**The Grand Canyon Conference on the Treatment of Addictive Behaviors.** South Rim of Grand Canyon. Tuesday-Saturday. Grand Canyon National Park Lodges. Hour-for-hour credit. Contact: T. P. Bouble, Conference Coordinator, Division of Continuing Education & Commity Services, University of New Mexico, Albuquerque, NM 87131. (505) 277-2931.

December 4-5—**Trauma Update '81.** Albuquerque. Friday-Saturday. Convention Center. 11 hours credit. Contact: Office of CME, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

December 11-12—**Annual Meeting New Mexico Chapter American College of Physicians and New Mexico Chapter American Society of Internal Medicine—Clinical Hematology and Oncology.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. 9 credit hours, also AAFP Prescribed. Contact: Robert J. Weller, MD, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7178.

February 22-26—**Taos Medical Symposium—Sports Medicine.** Taos. Monday-Friday. Kachina Lodge. 18 credit hours, also AAFP Prescribed. Contact: Dale A. Gray, MD, Taos Medical Symposium, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

February 26-28—**10th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 13 credit hours, also AAFP Prescribed. Contact: American Lung Association of New Mexico, 216 Truman NE, Albuquerque, NM 87108. (505) 265-0732.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 20 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

March 30-31—**Base Station Physician Course.** Taos. Tuesday-Wednesday. Sagebrush Inn. 9 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, NM Chapter American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 1-3—**New Mexico Chapter, American College of Emergency Physicians Meeting.** Taos. Thursday-Saturday. Sagebrush Inn. 18 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, 6320 Palma Pl. NW, Albuquerque, NM 87120.

November 17—**Pediatric Intensive Care Seminar.** Santa Fe. Tuesday. St. Vincent Hospital. 6.5 credit hours. Contact: Carol Luna, St. Vincent Hospital, Santa Fe, NM 87501. (505) 983-3361.

June 17-19—**Radiology Update—1982.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, lso AAFP Prescribed. Contact: Marcus J. Smith, MD, PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

November 20-22—**Gastroenterology Reading Retreat.** Abiquiu. Friday-Sunday. Ghost Ranch. 16 credit hours. Contact: Louis J. Levin, MD, NM Chapter, American College of Physicians, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health

Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

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FAMILY PRACTICE

February 8-12—**Thirteenth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

SURGERY

November 20—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

INTEREST TO ALL PHYSICIANS

November 12-13—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion at Jantzen Beach. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

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November 13-14—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Tri-Arc Travelodge. 17 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 581-7617.

December 4-5—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 17 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

December 10-12—**Dilemmas of Ethics and Health: Informed Consent Conference** (Sponsor: University of Utah). Park City. Thursday-Saturday. 11 hrs. Fee: $175. Contact: Claire Turner (801) 581-5809.

January 3-9—**9th Annual Symposium on Clinical Echocardiography** (Sponsors: American College of Cardiology/University of Utah). Snowbird. Sunday-Saturday. 22.5 hrs. Fee: $200-$300. Contact: A. D. Hagen, MD (801) 350-1185.

January 11-23—**Perinatal/Neonatal Administrative Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Monday-Saturday. Salt Lake Marriott. 58 hrs. Fee: $100-$300. Contact: Jean Thornton, RN (801) 581-7085.

January 13-14—**Diabetes Update** (Sponsor: Regional Medical Education Center/VA Hospital). Salt Lake City. Thursday-Friday. Hotel Utah. 15 hrs. Fee: $50. Contact: Nancy Harrison (801) 582-1565, ext. 1100.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 18 hrs. Fee: $245. Contact: Claire Turner (801) 581-7617.

January 22—**Anterior and Posterior Segment Photocoagulation** (Sponsor: University of Utah). Salt Lake City. Friday. Research Lecture Hall, UUMC. 6 hrs. Fee: $50. Contact: Mano Swartz, MD (801) 581-6384.

January 29-30—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

February 8-11—**11th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 32 hrs. Fee: $250. Contact: Linda Twitchell (801) 581-8633.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hotel Utah. 17 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-day-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 20-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 20-27—**The Snowbird Conference on Modern Diagnostic Methods in Internal Medicine.** (Sponsors: George Washington University Medical Center, Washington, DC/ Academy of Continuing Medical Education, Salt Lake City). Snowbird. Saturday-Saturday. 15 hrs. Fee: $245 (Residents: $150). Contact: Gregg P. Thomas, CME Office, George Washington University Medical Center, 2300 Eye Street, NW, Washington, DC 20037. (202) 676-4285.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain Pediatric Society Annual Scientific Meeting** (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

November 18—**Cadaver Kidney Retrieval.** Seattle. Wednesday. Virginia Mason Medical Center. Contact: VMMC.

November 18—**Ethical Issues in Medicine.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

November 18—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

November 19-20—**Current Urological Practice.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

November 19-20—**Office Urology for Primary Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

November 20—**Colon and Rectal Diseases.** Seattle. Friday. Park Hilton. Contact: U/W.

November 20-21—**Critically Ill Surgical Patient.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

November 21-28—**(HAWAII) Financial Planning for Physicians.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

November 30-December 2—**Noninvasive Diagnostic Methods.** Seattle. Monday-Wednesday. Park Hilton. Contact: U/W.

December 2, 9—**Ethical Issues in Medicine.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

December 3-4—**Update on Surgical Infections.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

December 3-4—**Alcoholism.** Yakima. Thursday-Friday. Memorial Hospital. Contact: U/W.

December 4—**Practical Pediatrics. Seattle.** Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5—**Medicine for Attorneys.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

December 9—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

December 10-11—**Aging and Elderly.** Seattle. Thursday-Friday. Washington Athletic Club. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

December 10-12—**Cytology Continuing Education Workshop.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: CME Harborview.

January 9-16—**(HAWAII) Endocrinology and Metabolism.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

January 14-15—**Sexual Disorders in Medical Practice.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 15—**Perspectives in Rheumatology and Clinical Immunology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 20—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

January 21-22—**Beta Block/Calcium Antagonists.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 28-29—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

January 28-30—**(OREGON) Cytology Continuing Education Workshop.** Portland. Thursday-Saturday. Contact: CME Harborview.

January 30-February 6—**(HAWAII) Office Urology for Urologists.** Maui. Saturday-Saturday. Hyatt Regency. Contact U/W.

January 31-February 7—**(MEXICO) Surgical Management of Trauma.** Puerto Vallarta. Sunday-Sunday. Camino Real. Contact: U/W.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 5-6—**Case Studies in Internal Medicine.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 6-13—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 12—**Nutrition in Hospitalized Patient.** Seattle. Friday. Park Hilton. Contact: U/W.

February 13-20—**(HAWAII) Plastic Surgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 13-20—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

February 20-27—**(HAWAII) Cardiology.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 1-2—**(CALIFORNIA) Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 1-2—**Computers in Continuing Education.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

March 4-5—**Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 6-13—**(IDAHO)—Perinatal Critical Care.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

March 6—**Handicapped Child.** Seattle. Saturday. Children's Orthopedic Medical Center. Contact: U/W.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 11-12—**Holistic Medicine.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18-19—**Depression and Anxiety.** Seattle. Thursday-Friday. Contact: U/W.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 27-April 3—**(HAWAII) Obstetrics and Gynecology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31—**Medicine and Civilization.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 21—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 22-23—**Vascular Diseases.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

April 29—**Trauma.** Seattle. Thursday. Museum of History and Industry. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hotel Utah. 17 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 20-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 20-27—**The Snowbird Conference on Modern Diagnostic Methods in Internal Medicine.** (Sponsors: George Washington University Medical Center, Washington, DC/ Academy of Continuing Medical Education, Salt Lake City). Snowbird. Saturday-Saturday. 15 hrs. Fee: $245 (Residents: $150). Contact: Gregg P. Thomas, CME Office, George Washington University Medical Center, 2300 Eye Street, NW, Washington, DC 20037. (202) 676-4285.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain Pediatric Society Annual Scientific Meeting** (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

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November 18—**Ethical Issues in Medicine.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

November 18—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

November 19-20—**Current Urological Practice.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

November 19-20—**Office Urology for Primary Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

November 20—**Colon and Rectal Diseases.** Seattle. Friday. Park Hilton. Contact: U/W.

November 20-21—**Critically Ill Surgical Patient.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

November 21-28—**(HAWAII) Financial Planning for Physicians.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

November 30-December 2—**Noninvasive Diagnostic Methods.** Seattle. Monday-Wednesday. Park Hilton. Contact: U/W.

December 2, 9—**Ethical Issues in Medicine.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

December 3-4—**Update on Surgical Infections.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

December 3-4—**Alcoholism.** Yakima. Thursday-Friday. Memorial Hospital. Contact: U/W.

December 4—**Practical Pediatrics. Seattle.** Friday. Virginia Mason Medical Center. Contact: VMMC.

December 5—**Medicine for Attorneys.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

December 9—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

December 10-11—**Aging and Elderly.** Seattle. Thursday-Friday. Washington Athletic Club. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

December 10-12—**Cytology Continuing Education Workshop.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: CME Harborview.

January 9-16—**(HAWAII) Endocrinology and Metabolism.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

January 14-15—**Sexual Disorders in Medical Practice.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 15—**Perspectives in Rheumatology and Clinical Immunology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 20—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

January 21-22—**Beta Block/Calcium Antagonists.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 28-29—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

January 28-30—**(OREGON) Cytology Continuing Education Workshop.** Portland. Thursday-Saturday. Contact: CME Harborview.

January 30-February 6—**(HAWAII) Office Urology for Urologists.** Maui. Saturday-Saturday. Hyatt Regency. Contact U/W.

January 31-February 7—**(MEXICO) Surgical Management of Trauma.** Puerto Vallarta. Sunday-Sunday. Camino Real. Contact: U/W.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 5-6—**Case Studies in Internal Medicine.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 6-13—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 12—**Nutrition in Hospitalized Patient.** Seattle. Friday. Park Hilton. Contact: U/W.

February 13-20—**(HAWAII) Plastic Surgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 13-20—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

February 20-27—**(HAWAII) Cardiology.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 1-2—**(CALIFORNIA) Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 1-2—**Computers in Continuing Education.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

March 4-5—**Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 6-13—**(IDAHO)—Perinatal Critical Care.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

March 6—**Handicapped Child.** Seattle. Saturday. Children's Orthopedic Medical Center. Contact: U/W.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 11-12—**Holistic Medicine.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18-19—**Depression and Anxiety.** Seattle. Thursday-Friday. Contact: U/W.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 27-April 3—**(HAWAII) Obstetrics and Gynecology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31—**Medicine and Civilization.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 21—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 22-23—**Vascular Diseases.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

April 29—**Trauma.** Seattle. Thursday. Museum of History and Industry. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1982—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: 1982—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1982—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1982—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1982—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: 1982—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: 1982—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: 1982—date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Midwinter Seminar January 7-9, 1982, Teton Village, Jackson. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

May 19—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

May 21-22—**Topics in Emergency Room Medicine: The First 60 Minutes.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 11-12—**Common Minor Surgeries.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

June 14-18—**Advances in Family Practice.** Seattle. Monday-Friday. Seattle Hilton. Contact: U/W.

June 17-19—**Medical Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact. U/W.

June 19-26—**(IDAHO) Radiology Northwest V.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Seattle Hilton. Contact: U/W.

June 23-27—**(OREGON) Ethics and History with Shakespeare.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

WYOMING

See Washington listing, September 16-18, 1982.

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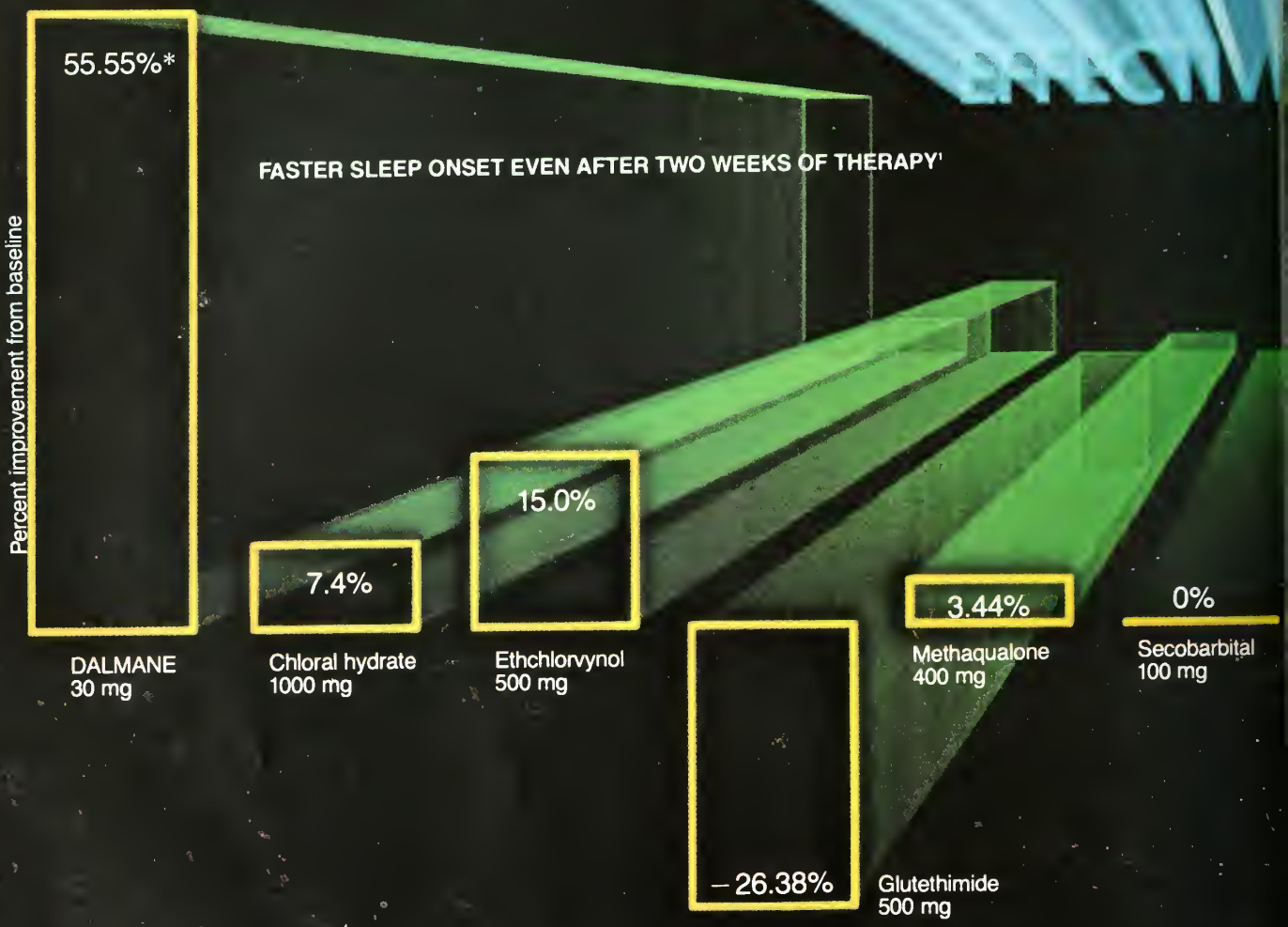

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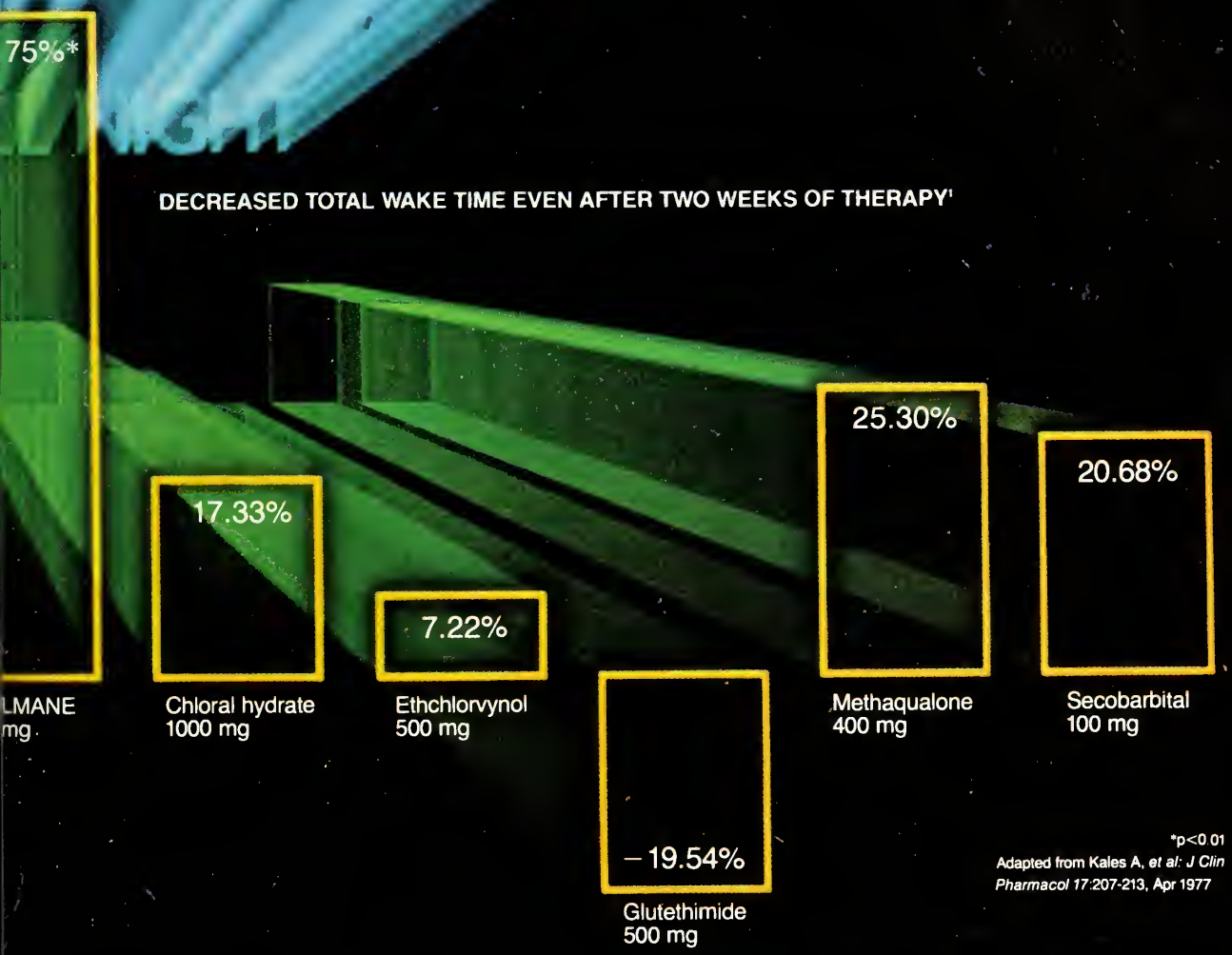

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Adapted from Kales A, *et al: J Clin Pharmacol* 17:207-213, Apr 1977

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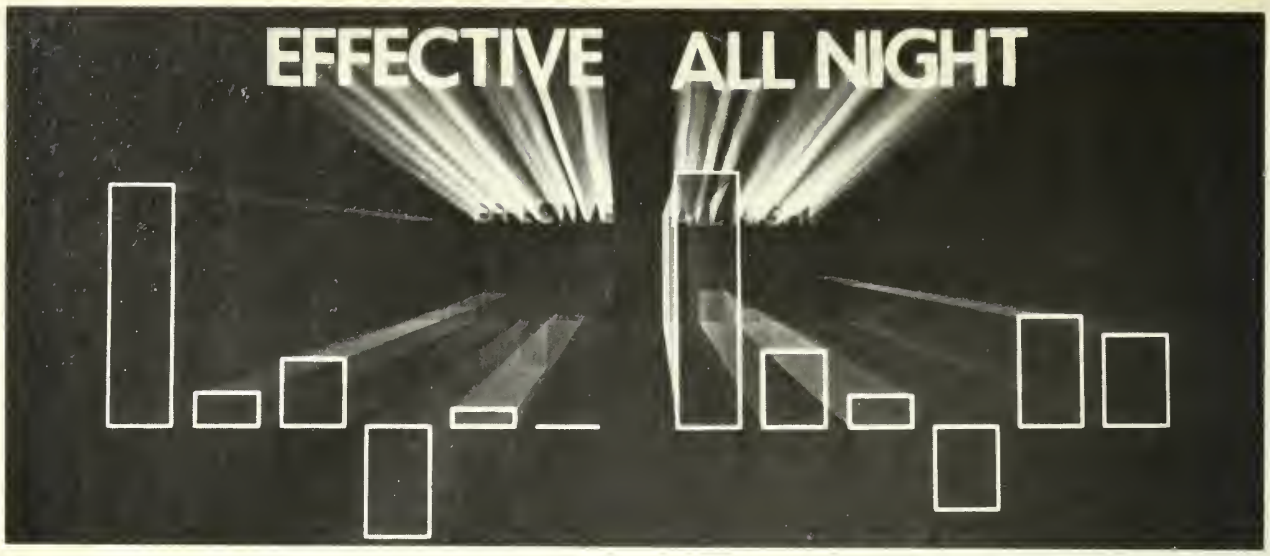

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UNLIKE NONSPECIFIC MEDICATIONS USED FOR SLEEP

Tricyclic antidepressants

–which are *not* sleep specific,[9] yet are sometimes used in nondepressed patients for sleep

–which can cause transient insomnia in the elderly[10]

–which can require careful monitoring in cardiovascular patients[10]

–which have strong anticholinergic effects[10]

Antihistamines

–which are *not* reliable sleep-inducing agents[11]

–which may produce stimulation instead[11]

–which have anticholinergic effects[11]

Major tranquilizers

–whose side effects may be troublesome for nonpsychotic patients[12]

–where tolerance for sedation appears rapidly[12]

Dalmane does not cause significant worsening of sleep beyond baseline levels upon discontinuation.[8]

References: **1.** Kales A, *et al. J Clin Pharmacol 17* 207-213, Apr 1977 **2.** Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **3.** Greenblatt DJ, Allen MD, Shader RI *Clin Pharmacol Ther 21* 355-361, Mar 1977 **4.** Moore JD, Weissman L *J Clin Pharmacol 16* 241-244, May-Jun 1976 **5.** Spiegel HE Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ 6. Robinson DS, Amidon EL. Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO New York, Raven Press, 1973, pp 641-646 **7.** Warfarin Study Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ **8.** Kales A, *et al Clin Pharmacol Ther 18* 356-363, Sep 1975 **9.** Baldessarini RJ Drugs and the treatment of psychiatric disorders, chap 19, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6 New York, Macmillan Publishing Co. Inc., 1980, pp. 391-447 **10.** Cole JO, Davis JM Antidepressant drugs, chap. 31 2, in *Comprehensive Textbook of Psychiatry II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2 Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp 1941-1956 **11.** Douglas WW Histamine and 5-hydroxytryptamine (serotonin) and their antagonists, chap. 26, in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, ed 6 New York, Macmillan Publishing Co Inc., 1980, pp. 609-646 **12.** Davis JM, Cole JO Antipsychotic drugs, chap. 31 1, in *Comprehensive Textbook of Psychiatry II*, edited by Freedman AM, Kaplan HI, Sadock BJ, ed 2 Baltimore, The Williams & Wilkins Company, vol 2, 1976, pp 1921-1940

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect.
Adults: 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients*: 15 mg recommended initially until response is determined.

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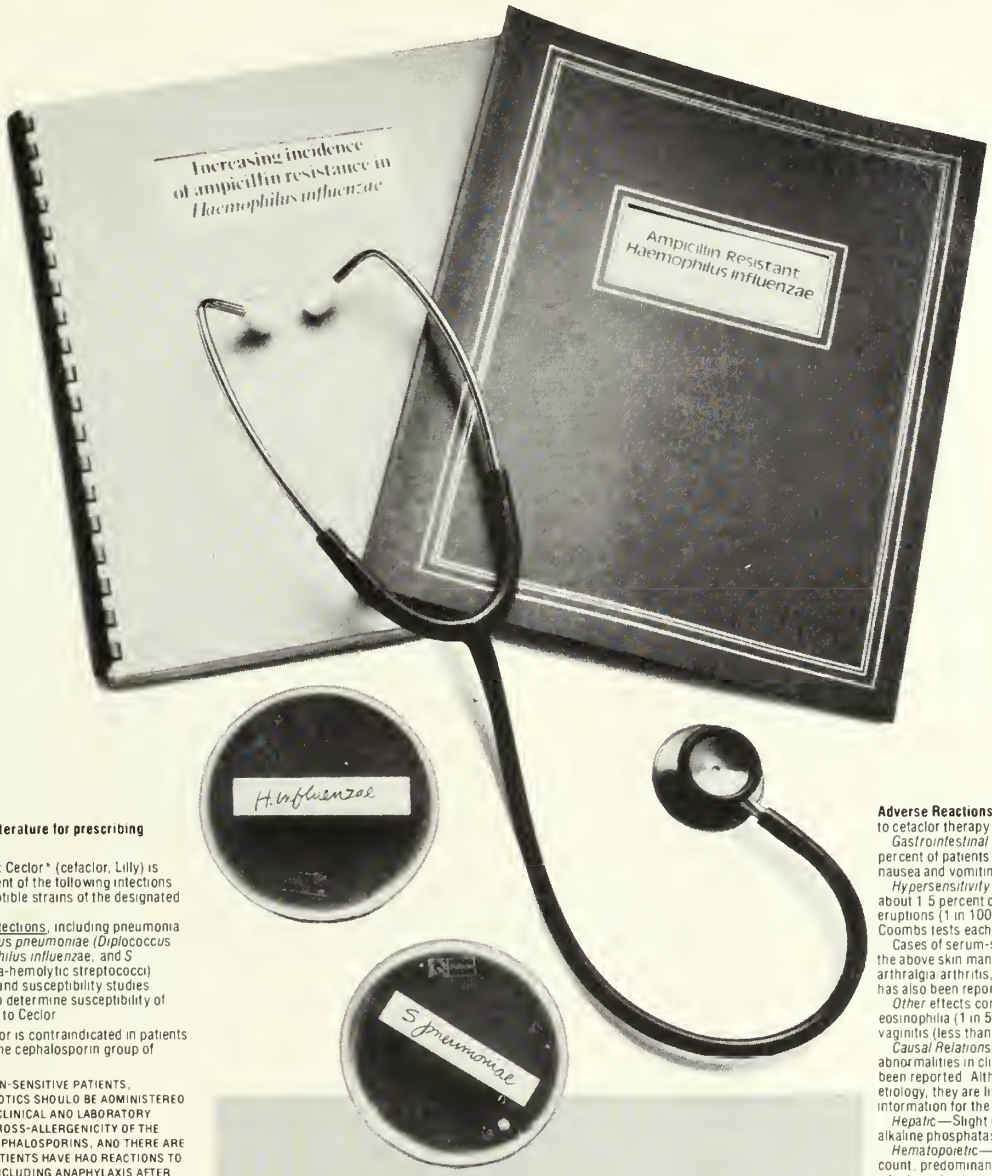
An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

ief Summary.
onsult the package literature for prescribing formation.

dications and Usage: Ceclor® (cefaclor, Lilly) is icated in the treatment of the following infections hen caused by susceptible strains of the designated icroorganisms.
Lower respiratory infections, including pneumonia used by *Streptococcus pneumoniae (Diplococcus eumoniae), Haemophilus influenzae*, and *S ogenes* (group A beta-hemolytic streptococci) Appropriate culture and susceptibility studies ould be performed to determine susceptibility of e causative organism to Ceclor

ntraindication: Ceclor is contraindicated in patients th known allergy to the cephalosporin group of tibiotics

arnings: IN PENICILLIN-SENSITIVE PATIENTS, PHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED AUTIOUSLY THERE IS CLINICAL AND LABORATORY IDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE NICILLINS AND THE CEPHALOSPORINS, AND THERE ARE STANCES IN WHICH PATIENTS HAVE HAD REACTIONS TO TH DRUG CLASSES (INCLUDING ANAPHYLAXIS AFTER RENTERAL USE).
Antibiotics, including Ceclor, should be administered utiously to any patient who has demonstrated some rm of allergy, particularly to drugs

ecautions: If an allergic reaction to cefaclor occurs, e drug should be discontinued, and, if necessary, the tient should be treated with appropriate agents, e g , essor amines, antihistamines, or corticosteroids
Prolonged use of cefaclor may result in the ergrowth of nonsusceptible organisms Careful servation of the patient is essential If superinfection curs during therapy, appropriate measures should taken
Positive direct Coombs tests have been reported uring treatment with the cephalosporin antibiotics In ematologic studies or in transfusion cross-matching ocedures when antiglobulin tests are performed on e minor side or in Coombs testing of newborns hose mothers have received cephalosporin antibiotics efore parturition, it should be recognized that a sitive Coombs test may be due to the drug
Ceclor should be administered with caution in the esence of markedly impaired renal function. Under ich a condition, careful clinical observation and boratory studies should be made because safe sage may be lower than that usually recommended
As a result of administration of Ceclor, a false-sitive reaction for glucose in the urine may occur is has been observed with Benedict's and Fehling's lutions and also with Clinitest® tablets but not with s-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)
Usage in Pregnancy—Although no teratogenic or nfertility effects were seen in reproduction studies mice and rats receiving up to 12 times the aximum human dose or in ferrets given three times e maximum human dose, the safety of this drug for se in human pregnancy has not been established he benefits of the drug in pregnant women should e weighed against a possible risk to the fetus
Usage in Infancy—Safety of this product for use in fants less than one month of age has not been stablished

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below
Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90)
Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients
Cases of serum-sickness-like reactions, including the above skin manifestations, fever, and arthralgia/arthritis, have been reported Anaphylaxis has also been reported
Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)
Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician
Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)
Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)
Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200) [103080R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae* ®

Note Ceclor® (cefaclor) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients
Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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8 Principles and Practice of Infectious Diseases (edited by G L Mandell, R G Douglas, Jr , and J E Bennett), p 487 New York John Wiley & Sons 1979

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Dr. Ouslander is Adjunct Assistant Professor of Medicine, Department of Medicine, and a Fellow in Geriatric Medicine, UCLA Multicampus Division of Geriatric Medicine, Department of Medicine, UCLA School of Medicine, Los Angeles; he is affiliated with the Geriatric Research, Education, and Clinical Center, Sepulveda Veterans Administration Medical Center, Sepulveda, California.

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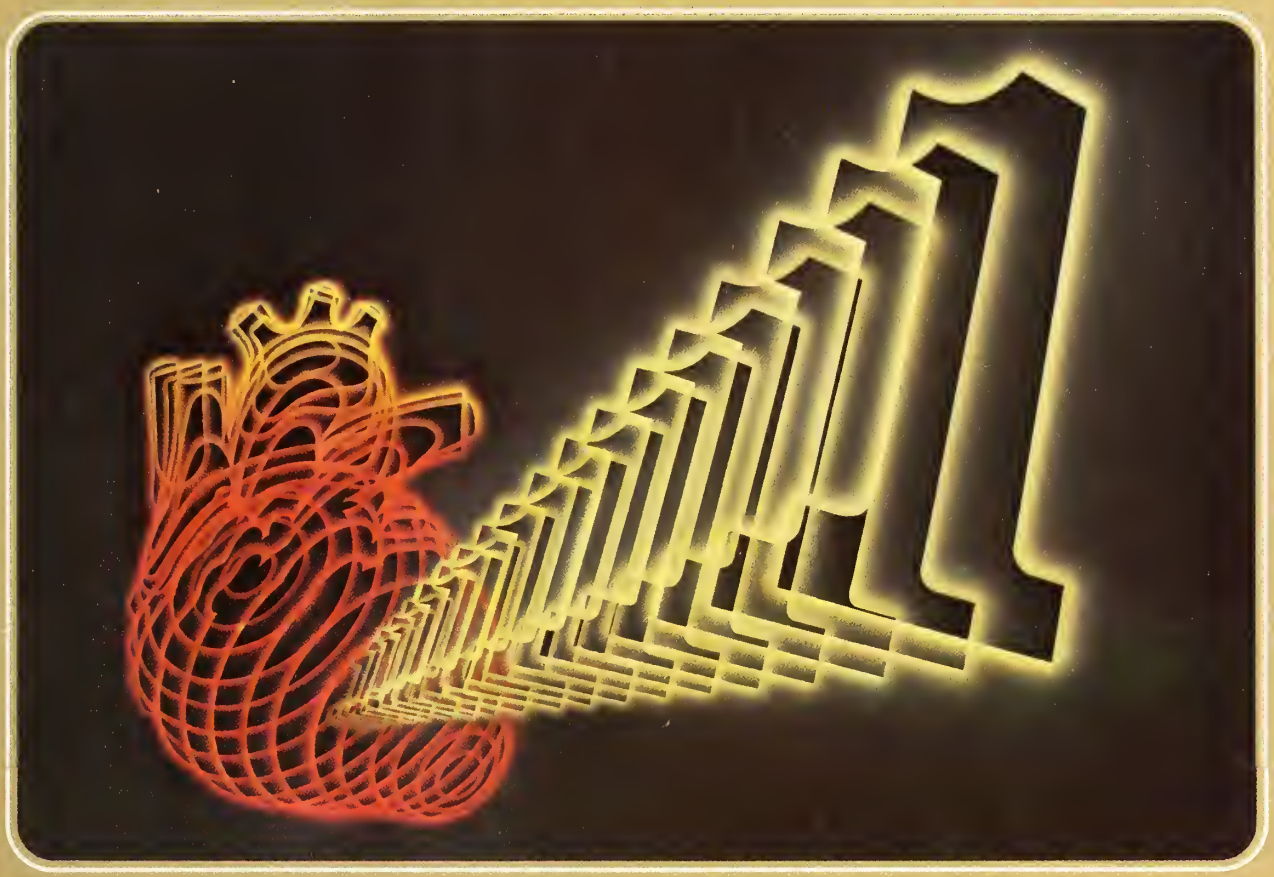
CORGARD®
nadolol tablets



The first beta-blocker with once-a-day dosage

Round-the-clock protection in the control of hypertension

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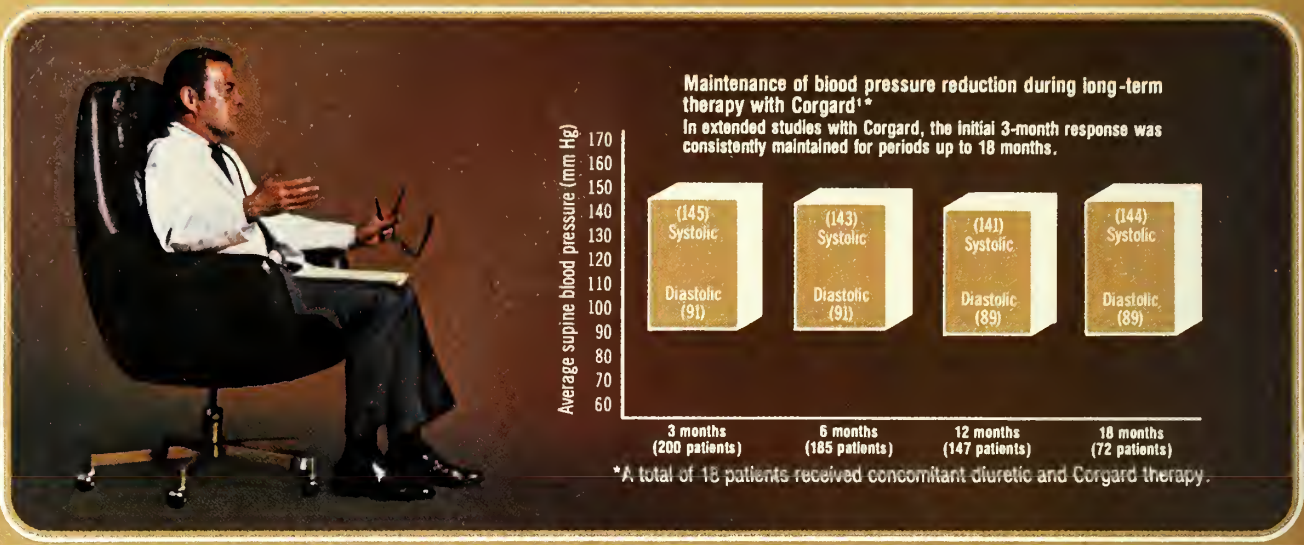
See last page of this advertisement for brief summary.



When you prescribe...

CORGARD® (nadolol tablets) ...for significant blood pressure reduction

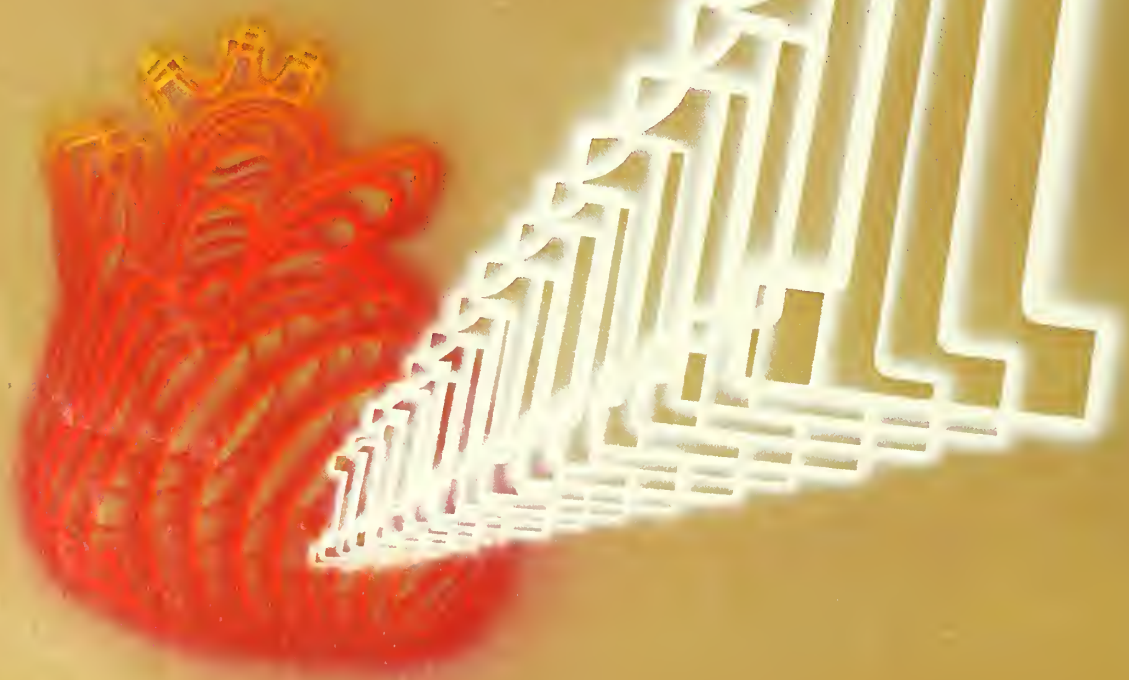
In short-term clinical studies of 114 patients with mild, moderate and severe hypertension, Corgard taken in single daily doses of 40–320 mg (mean: 200 mg) achieved a significant overall reduction in supine and standing blood pressure in 94% of patients — this included 62.3% of the patients who achieved normalized supine diastolic pressure (≤ 90 mm Hg).

...for comparable efficacy, once a day, to propranolol, four times a day

In a controlled clinical comparison of 179 patients with mild, moderate and severe hypertension, Corgard, once a day, was as effective in reducing supine and standing pressure as propranolol, four times a day.[1]

...for extended protection in control of mild, moderate and severe hypertension

Corgard provides round-the-clock control of hypertension by reducing elevated systolic and diastolic blood pressure — with a single daily dose.



They can comply.

CORGARD® [nadolol tablets] ...promotes compliance with a single daily dose

The 20- to 24-hour serum half-life of Corgard offers round-the-clock reduction in blood pressure with a once-daily dosage. With no need to interrupt daily activities to take multiple doses of medication, patients are more likely to comply.

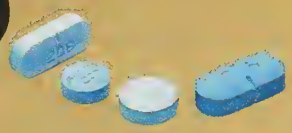
...is often effective alone, without a diuretic[1]

Control of blood pressure with a single agent also simplifies the patient's medication schedule. Only one medication once a day means less likelihood of forgotten or skipped doses.

...rarely causes impotence, loss of libido, orthostatic hypotension*

Because it is virtually free from these undesirable side effects, the patient can function normally, without undue concern.

Prescribe CORGARD® nadolol tablets



40 mg, 80 mg, 120 mg, and 160 mg tablets

The common-sense beta-blocker for hypertension

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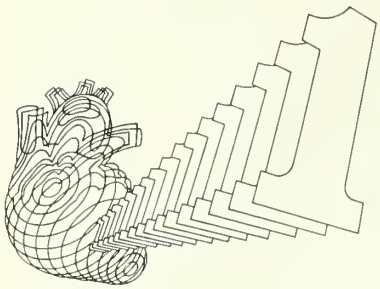
Please see brief summary for discussion of Contraindications, Adverse Reactions, Precautions, and Warnings, including avoidance of abrupt withdrawal, on next page of this advertisement.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets
DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic po tial was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Bec many drugs are excreted in human milk, exercise caution when nadolol is administered nursing woman. Animal studies showed that nadolol is found in the milk of lactating

Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and h rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute o commonly, and heart rates below 40 beats per minute and/or symptomatic bradyca were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, us of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac fail hypotension, and rhythm/conduction disturbances have each occurred in about 1 of patients. Single instances of first degree and third degree heart block have been repo intensification of AV block is a known effect of beta-blockers (see also CONTRAIN DICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedati and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICA TIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discom fort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, s disturbances have been reported. The oculomucocutaneous syndrome associated wit practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other bet adrenergic blocking agents have not been reported with nadolol, they should be consic potential adverse effects of nadolol. **Central Nervous System** — reversible mental de sion progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory lo emotional lability with slightly clouded sensorium; decreased performance on neuro-psychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpu **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory dis **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodia In addition to gastric lavage, employ the following measures as appropriate. In dete mining duration of corrective therapy, take note of long duration of effect of nadol

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no resp to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been repor that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (Ther evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 increments at 3 to 7 day intervals until optimum clinical response or pronounced sl of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respon mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 increments until optimum blood pressure reduction is achieved; usual maintenance is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package in for dosage in these patients.

For full prescribing information, consult package insert.
HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol pe tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tal

Reference:
1. Data on file, Squibb Institute for Medical Research.

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LAWRENCE Z. FEIGENBAUM, MD; CAROL L. ALLEN, MA, and HAROLD BROWNSTEIN, MD
Dr. Feigenbaum is Director of Professional Services and Medical Education, and Medical Training Director, Geriatric Services, Mount Zion Hospital and Medical Center, San Francisco; and Clinical Professor of Medicine and Associate Dean for Interinstitutional Programs, University of California, San Francisco, School of Medicine. Ms. Allen is Interinstitutional Grants Coordinator, Mount Zion Hospital and Medical Center, San Francisco. Dr. Brownstein is Director of Ambulatory Services and Medical Director, Geriatric Services, Mount Zion Hospital and Medical Center, San Francisco; and Associate Clinical Professor of Medicine, University of California, San Francisco, School of Medicine.

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LAURENCE Z. RUBENSTEIN, MD, MPH
Dr. Rubenstein is Chief, Geriatric Evaluation Unit, and Assistant Clinical Director, Geriatric Research, Education, and Clinical Center, Sepulveda Veterans Administration Medical Center, Sepulveda, California; and Assistant Professor of Medicine, UCLA School of Medicine, Los Angeles.

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Dr. R. L. Kane is a Senior Researcher, The Rand Corporation, Santa Monica, California, and Professor of Medicine, Multicampus Division of Geriatric Medicine, Department of Medicine, UCLA School of Medicine, Los Angeles. Dr. R. A. Kane is a Social Scientist at The Rand Corporation, Santa Monica, California.

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Dr. Estes is Professor of Sociology, and Director, Aging Health Policy Center, School of Nursing, University of California, San Francisco. Dr. Lee is Professor of Social Medicine, and Director, Institute for Health Policy Studies, School of Medicine, University of California, San Francisco.

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Dr. Martin is Professor of Medicine and Biochemistry, University of California, San Francisco, School of Medicine.

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Dr. Scoggin is Associate Professor of Medicine (Pulmonary Sciences) and Head, Section on Human Genetics, Department of Medicine, University of Colorado School of Medicine; and Institute Fellow, Eleanor Roosevelt Institute for Cancer Research, The Florence R. Sabin Laboratories for Genetic and Developmental Medicine, University of Colorado Health Sciences Center, Denver.

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Dr. Bergeson is from the Department of Pediatrics, Good Samaritan Hospital, Phoenix, Arizona. Dr. Smith is from the Department of Surgery, University of Oklahoma College of Medicine and the Oklahoma Children's Memorial Hospital, Oklahoma City.

530 *In Memoriam*

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The editors acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given to the journal during the past year.

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Cover illustration by
DAVID G. LARSON

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 19)**

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association**

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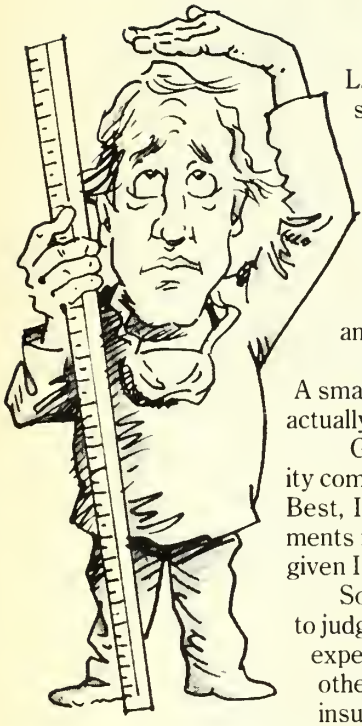

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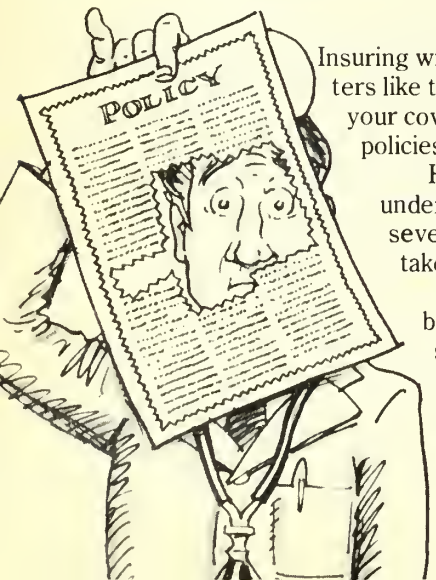

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TRUTHS, AND ACTS ABOUT INSURANCE.

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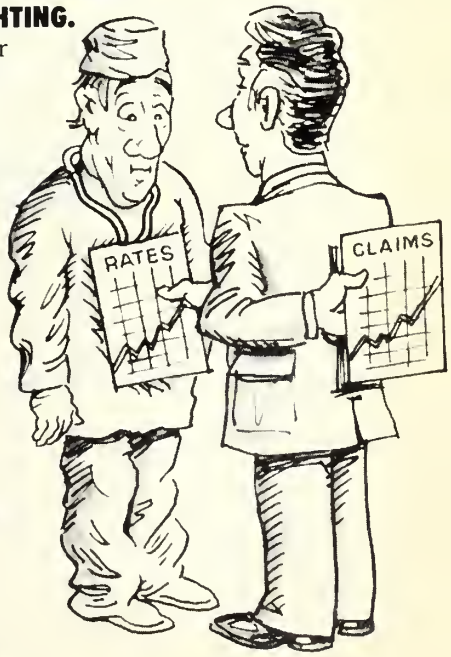

For more facts, contact: Insurance Corporation of America, ICA Center, 4295 San Felipe, Box 56308, Houston, Texas 77027. 1-800-231-2615. In Texas 1-800-392-9702. (Check for availability in your state.)

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(Continued on Page 30)

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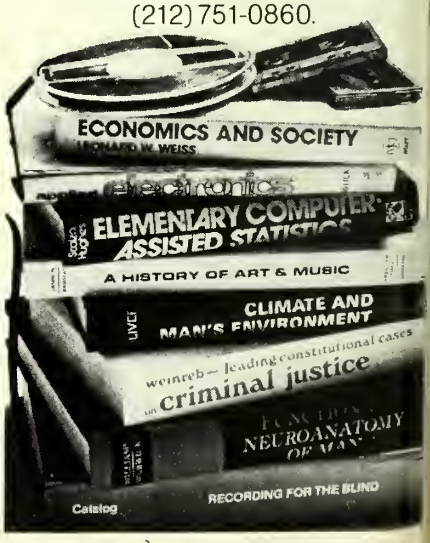

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ANESTHESIOLOGY

January 7-10—**Anesthesiology Update.** UCSD at Hotel del Coronado, Coronado. Thursday-Sunday.

January 29-31—**20th Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Fndn., Childrens Hospital of Los Angeles, at Marriott, Los Angeles. Friday-Sunday. 15 hrs. $185. Contact: Wayne Herbert, MD, Prog. Dir., Pediatric Anesthesiology Fndn., P.O. Box 54700, Los Angeles 90054. (213) 669-2262.

March 14-18—**International Anesthesia Research Society—56th Congress.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: International Anesthesia Research Soc., 3645 Warrensville Center Rd., Cleveland, OH 44122. (216) 295-1124.

March 17-21—**American Society of Regional Anesthesia.** Del Monte Hyatt, Monterey. Wednesday-Sunday. 16 hrs. $175. Contact: Gale Thompson, MD, ASRA, P.O. Box 11083, Richmond, VA 23230. (804) 358-0305.

March 21-26—**Anesthesiology 1982—8th Annual Winter Meeting.** Anesthesiology Educational Foundation at Sierra Nevada Inn, Mammoth Lakes. Sunday-Friday. Contact: AEF, P.O. Box 24230, Los Angeles 90024.

April 3-10—**10th Obstetric Anesthesia Conference.** Dept. of Anesthesiology, Ohio State Univ. College of Medicine, at Sheraton Waikiki, Oahu, Hawaii. One week. 25 hrs. Contact: Dept. of Anesthesiology, c/o Bradford Travel, 1200 W. Henderson Rd., Columbus, OH 43220. (614) 457-9990 or (614) 421-8487 (OSU).

CANCER

December 16—**17th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

January 29-31—**Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Diane L. Johnson, L.A. Radiological Soc., P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 24-26—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF. Wednesday-Friday.

February 27-28—**Breast Cancer: Conservation Surgery and Radiation Therapy Now—17th Annual San Francisco Cancer Symposium.** West Coast Cancer Fndn.; Am. Cancer Soc., Calif. Div.; St. Mary's Hosp. and Med. Ctr. at Sheraton Fisherman's Wharf, San Francisco. Saturday-Sunday. 12 hrs. $115 before Jan. 1; $140, thereafter. Contact: West Coast Cancer Fndn., 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 22-24—**Bladder Cancer.** American Urological Assn. at Biltmore Hotel, Los Angeles. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, AUA Office of Education, P.O. Box 25147, Houston, TX 77005.

EMERGENCY MEDICINE

January 18-22—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

January 23-30—**Controversies and Problems in Emergency Medicine.** UCSD at Hawaii. One week.

January 25-29—**Topics in Emergency Medicine.** UCSF. Monday-Friday.

February 5-6—**Base Station Physician Symposium.** Calif. Chapter, Am. College of Emergency Physicians, at Ahwahnee Hotel, Yosemite. Friday-Saturday. 9 hrs. $125, ACEP members; $150, nonmembers. Contact: CAL/ACEP, 8639 Lincoln Blvd., #240, Los Angeles 90045. (213) 776-1820.

February 7-12—**Winter Sports Injuries.** See Of Interest to All, February 7-12.

(Continued on Page 23)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
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STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

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Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

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2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare[5,6] This risk has been estimated as not greater than 4 per 1000 exposures Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects[13-16] One case control study[16] estimated a 4 7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some of these exposures were very short and involved only a few days of treatment The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000 In the past female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U S P) for oral administration contains a mixture of estrogens obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine It contains estrone, equilin, and 17α-dihydroequilin together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications for use as follows

Effective:

1 Moderate to severe *vasomotor* symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions)

2 Atrophic vaginitis

3 Kraurosis vulvae

4 Female hypogonadism

5 Female castration

6 Primary ovarian failure

7 Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease

8 Prostatic carcinoma – palliative therapy of advanced disease

9 Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens[14]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)

"Probably" effective: For estrogen deficiency induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures Final classification of this indication requires further investigation

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions 1 Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease 2 Known or suspected estrogen-dependent neoplasia 3 Known or suspected pregnancy (See Boxed Warning) 4 Undiagnosed abnormal genital bleeding 5 Active thrombophlebitis or thromboembolic disorders 6 A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy)

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms A recent study has reported a 2 to 3 fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens[19]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement[14,20] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis pulmonary embolism, stroke, and myocardial infarction[21-26] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users[27,28] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives[29,30] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nontatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc Oral contraceptives appear to be associated with an increased incidence of mental depression[2,38] Patients with a history of depression should be carefully observed Preexisting uterine leiomyomata may increase in size during estrogen use The pathologist should be advised of estrogen therapy when relevant specimens are submitted If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen

a Increased sulfobromophthalein retention

b Increased prothrombin and factors VII, VIII, IX, and X decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered

d Impaired glucose tolerance

e Decreased pregnanediol excretion

f Reduced response to metyrapone test

g Reduced serum folate concentration

h Increased serum triglyceride and phospholipid concentration

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts), nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, chloasma or metasma which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females

DOSAGE AND ADMINISTRATION: 1 *Given cyclically for short term use only* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0 3 to 1 25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e g, three weeks on and one week off)

Attempts to discontinue or taper medication should be made at three to six month intervals

2 *Given cyclically* Female hypogonadism Female castration Primary ovarian failure Osteoporosis

Female hypogonadism – 2 5 to 7 5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration If bleeding does not occur by the end of this period, the same dosage schedule is repeated The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U S P), 2 5 to 7 5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure – 1 25 mg daily, cyclically Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control

Osteoporosis (to retard progression) – 1 25 mg daily, cyclically

3 *Given for a few days* Prevention of postpartum breast engorgement – 3 75 mg every four hours for five doses, or 1 25 mg every four hours for five days

4 *Given chronically* Inoperable progressing prostatic cancer – 1 25 to 2 5 mg three times daily

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U S P) No 865 – Each *purple* tablet contains 2 5 mg in bottles of 100 and 1,000 No 866 – Each *yellow* tablet contains 1 25 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 867 – Each *red* tablet contains 0 625 mg in bottles of 100 and 1,000 Also in unit dose package of 100 No 868 – Each *green* tablet contains 0 3 mg in bottles of 100 and 1,000

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New York, N Y 10017

(Continued from Page 19)

February 12-13—**Toxicologic and Infectious Disease Emergencies.** UCLA. Friday-Saturday.

February 28-March 5—**Emergency Medicine.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

March 7-10—**Sports Injuries Update.** UCD at Hyatt, Lake Tahoe. Sunday-Wednesday.

March 14-19—**Third Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI at Mammoth Lakes. Sunday-Friday. 25 hrs. $290. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 540-9876.

March 15-19—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD at Islandia Hotel, San Diego. Monday-Friday. 36 hrs. $425.

April 10-17—**Pediatric Emergencies.** UCSD at Kauai, Hawaii. One week. 21 hrs. $325.

April 24-May 2—**Emergency Medicine.** USC at Hawaii. One week. 25 hrs. $425.

May 10-14—**Postgraduate Institute for Emergency Room Physicians, Symposium I.** UCSD. Monday-Friday. 36 hrs. $425.

MEDICINE

January-March—**Endocrinology for the Practicing Internist.** UCLA. Wednesday evenings.

January 8-15—**6th Annual Echocardiography Conference.** Honolulu Medical Group Research and Education Fndn. at Kauai Surf Resort, Kauai. One week. 32 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

January 9-15—**Gastrointestinal and Hepatic Diseases.** Honolulu Medical Group Research and Education Fndn. at Hyatt Regency, Maui. Saturday-Friday. 21 hrs. Contact: Honolulu Med. Grp. Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 9-16—**Endocrinology and Metabolism.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

January 13—**Rheumatology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

January 13—**Jaundice—Modern Diagnosis.** LLU. Wednesday. 4 hrs.

January 16-23—**Nephrology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $425.

January 20-23—**Conference on Nephrology and Hypertension.** UCSD at Hilton, San Diego. Wednesday-Saturday.

January 27-29—**Echocardiography: An Introductory Course for the Practicing Physician.** American College of Cardiology and UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 2-6—**What Is Ahead in Lung Diseases for the 80's.** USC at Death Valley. Tuesday-Saturday.

February 3-5—**Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 6—**Clinics in Medicine—Rheumatology.** PMC. Saturday. 3 hrs. $40.

February 12-13—**Rheumatology Medicine.** UCD. Friday-Saturday.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

February 17-19—**Recent Advances in Noninvasive Cardiac Imaging: Applications in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Wednesday-Friday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

February 18-20—**Controversies and Problem Solving With Endoscopy—An Update.** So. Calif. Society for Gastrointestinal Endoscopy at Beverly Hilton Hotel, Beverly Hills. Thursday-Saturday. 18 hrs. Contact: Dr. Albert Dreskin, 13652 Cantara St., Panorama City 91402.

February 20-27—**Cardiology.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Sunday-Tuesday.

February 25-28—**Federation of the Western Societies of Neurological Science.** Hotel del Coronado, Coronado. Thursday-Sunday. 15 hrs. Contact: Renee Kaseff, 525 Hurlingham Ave., San Mateo 94402. (415) 344-9082.

February 26—**A Day in Nephrology.** Sutter Community Hospitals at Holidome Convention Center, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 27-28—**Immunology.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Basic Neuroscience.** STAN. Saturday-Sunday. 12 hrs. $225.

February 27-28—**Asthma: Impact and Strategies for Change.** UCLA. Saturday-Sunday. 14 hrs. $85.

March 3-6—**Third World Congress for Bronchology.** World Assn. for Bronchology and American College of Chest Physicians at Town and Country, San Diego. Wednesday-Saturday. $250, WAB and ACCP members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 3-6—**Immunology and the Clinical Practice of Allergy—6th Annual Course.** UCSD at Hilton Hotel, San Diego. Wednesday-Saturday. 20 hrs.

March 3-6—**Third World Congress for Bronchology.** American College of Chest Physicians and World Assn. for Bronchology at Town and Country Hotel, San Diego. Wednesday-Saturday. $250, ACCP and WAB members; $300, nonmembers. Contact: ACCP, P.O. Box 93826, Chicago 60670. (312) 698-2200.

March 5—**Diabetes.** UCD at Red Lion Inn, Sacramento. Friday.

March 6—**Cardiology for the Primary Care Physician II: Office Diagnosis of the Cardiac Patient.** PMC. Saturday. 6 hrs. $95.

March 7-10—**Basic Cardiology for the Practicing Physician.** UCSF at Lake Tahoe. Sunday-Wednesday.

March 10—**Hypothyroidism—Unmasked.** LLU. Wednesday. 4 hrs. $30.

March 11-13—**Therapeutic and Diagnostic Uses of the Cardiac Catheter.** Am. College of Cardiology at Bonaventure Hotel, Los Angeles. Thursday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 12-13—**Exercise Stress Testing: Today and Tomorrow.** American College of Cardiology at Memorial Hospital Medical Center, Long Beach. Friday-Saturday. Contact: Registration Secretary, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

March 12-14—**Western Institute on Epilepsy.** UCLA at Marriott, Los Angeles. Friday-Sunday. $60.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

(Continued on Page 40)

New from Janssen Pharmaceutica: Introducing a promising new approach to coccidioidomycosis therapy

NIZORAL™ TABLETS (ketoconazole)

New:

the first and only orally effective, broad-spectrum antifungal agent.

NIZORAL (ketoconazole) is clinically effective against the major yeast and fungal pathogens. For *C. immitis,* the average MIC is less than 1 μg/ml. Absorption of ketoconazole is rapid; mean peak plasma levels of approximately 3.5 μg/ml are reached within 1-2 hours following a single 200 mg tablet. Development of resistance to NIZORAL has not yet been reported.

Effective:

"...a promising new drug for treatment of coccidioidomycosis."[1]

Clinical studies employing 200 to 400 mg NIZORAL per day have shown a combined response rate* of 35% after 26 (median) weeks of therapy; (at this point, however, 69% of patients were still being treated). Most patients were severe and chronic cases, either failures on or intolerant to amphotericin B.[2] (Recommended minimum treatment is 180 days.)

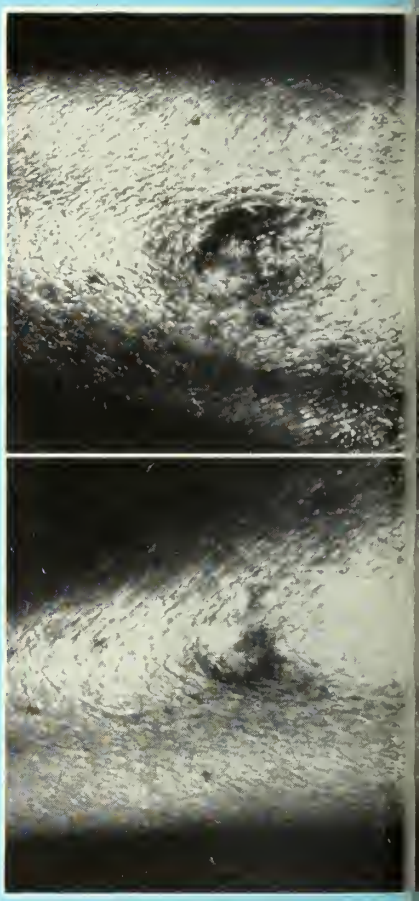
Safe:

"...can be safely administered for prolonged periods..."[3]

Freedom from long-term toxicity permits use of extended therapeutic courses of NIZORAL, when indicated, and provides an extra margin of safety in presumptive antifungal therapy. Long-term administration has revealed no organ toxicity and no consistent changes in important hematological or biochemical values. Infrequent, transient increases in serum liver enzymes have been seen. Adverse reactions were generally minor and only rarely required withdrawal of therapy.

Convenient:

once-a-day oral regimen fosters compliance...facilitates use both in and out of the hospital.



Top: Cutaneous lesion, disseminated coccidioidomycosis, before therapy.

Bottom: Lesion markedly resolved after oral NIZORAL therapy; photographed at 18 months.

*Includes cases in remission or markedly improved (no evidence of active disease); both mycological and clinical criteria were considered in measuring overall response.

For further information on NIZORAL write: Professional Services, Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903.

See the facing page for Complete Prescribing Information.

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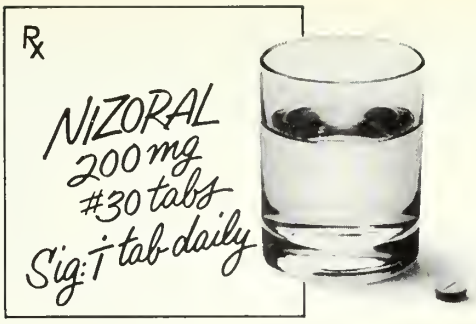
JANSSEN PHARMACEUTICA

NEW orally effective

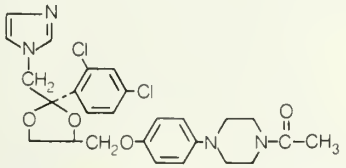
NIZORAL™ TABLETS (ketoconazole)

One tablet a day provides broad-spectrum antimycotic efficacy



DESCRIPTION

NIZORAL™ (ketoconazole) is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole. Ketoconazole is *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:



NIZORAL™ is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44.

CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately 3.5 μg/ml are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL™ is converted into several inactive metabolites. The major identified metabolic pathways are: oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99%, mainly to the albumin fraction. Only a negligible proportion of NIZORAL™ reaches the cerebral spinal fluid. NIZORAL™ is a weak dibasic agent and thus requires acidity for dissolution and absorption.

NIZORAL™ is active against clinical infections with *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Phialophora* spp. Development of resistance to NIZORAL™ has not yet been reported.

The following preclinical data are available; however, their clinical significance is unknown. NIZORAL™ is active *in vitro* against dermatophytes, dimorphic fungi, eumycetes, yeasts, actinomycetes, phycomycetes and various other fungi. In animal models, activity has been demonstrated against *Candida* spp., dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Coccidioides immitis*, and *Cryptococcus neoformans*.

Mode of Action: *In vitro* studies suggest that NIZORAL™ impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. Tests in animals suggest this mechanism is not important in mammalian cells.

INDICATIONS AND USAGE

NIZORAL™ is indicated for the treatment of the following fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL™ should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

For the initial diagnosis, the infective organism should be identified; however, therapy may be initiated prior to obtaining laboratory results.

CONTRAINDICATIONS

NIZORAL™ is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

General: In four subjects with drug-induced achlorhydria, a marked reduction in NIZORAL™ absorption was observed. NIZORAL™ requires acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least two hours after NIZORAL™ administration. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a glass or plastic straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Drug Interactions: There is no evidence for clinically significant interaction with oral anticoagulant or oral hypoglycemic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of NIZORAL™ as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames' *Salmonella* microsomal activator assay was also negative.

Pregnancy: Teratogenic effects: *Pregnancy Category C*. NIZORAL™ has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day, (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

Nonteratogenic effects: NIZORAL™ has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation.

In addition, dystocia (difficult labor) was noted in rats administered NIZORAL™ during the third trimester of gestation. This occurred when NIZORAL™ was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of NIZORAL™ during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD_{50} of NIZORAL™ given by gavage to the female rat is 166 mg/kg, whereas in the male rat the oral LD_{50} is 287 mg/kg.

Nursing Mothers: Since NIZORAL™ is probably excreted in the milk, mothers who are under NIZORAL™ treatment should not breast-feed the child.

Pediatric Use: Safety in children under two years of age has been documented in a limited number of cases.

ADVERSE REACTIONS

NIZORAL™ is usually well tolerated. Most adverse reactions reported have been mild and transient and have only rarely required withdrawal of therapy.

The most frequent adverse reactions were nausea and/or vomiting, which occurred in approximately 3% of patients. Abdominal pain was reported in approximately 1.2% of patients; pruritus in approximately 1.5% of patients. The following have been reported in less than 1% of patients: headache, dizziness, somnolence, fever and chills, photophobia, and diarrhea. Infrequent, transient increases in serum liver enzymes have been seen.

OVERDOSAGE

In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting dose of NIZORAL™ is a single daily administration of 200 mg (one tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of NIZORAL™ may be increased to 400 mg (two tablets) once daily.

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Children weighing 20 kg or less: . . . . . 50 mg (¼ tablet) once daily
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Generally, treatment should be continued until all clinical and laboratory tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is one or two weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is six months.

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For:
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References:
1. Brass C, Galgiani JN, Campbell SC, et al: Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. *Reviews of Infectious Diseases* 2 (4): 656-660, 1980. **2.** Data on file, Janssen Pharmaceutica **3.** Graybill JR, Lundberg D, Donovan W, et al: Treatment of coccidioidomycosis with ketoconazole: Clinical and laboratory studies of 18 patients. *Reviews of Infectious Diseases* 2 (4): 661-673, 1980.

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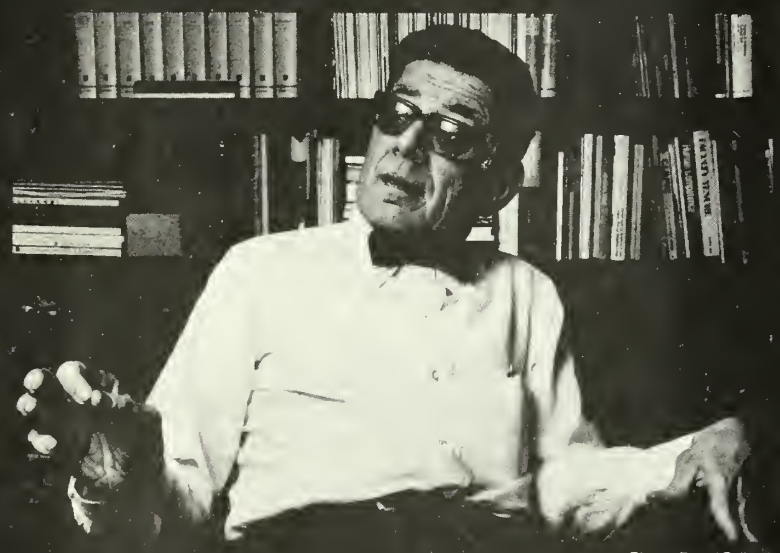

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"Here" is Hofstra University and Dr. Harold E. Yuker is its provost. "I never dreamed of being a college administrator. I'm the number two person and responsible for a budget of over a million dollars. When the president is away, I run the place."

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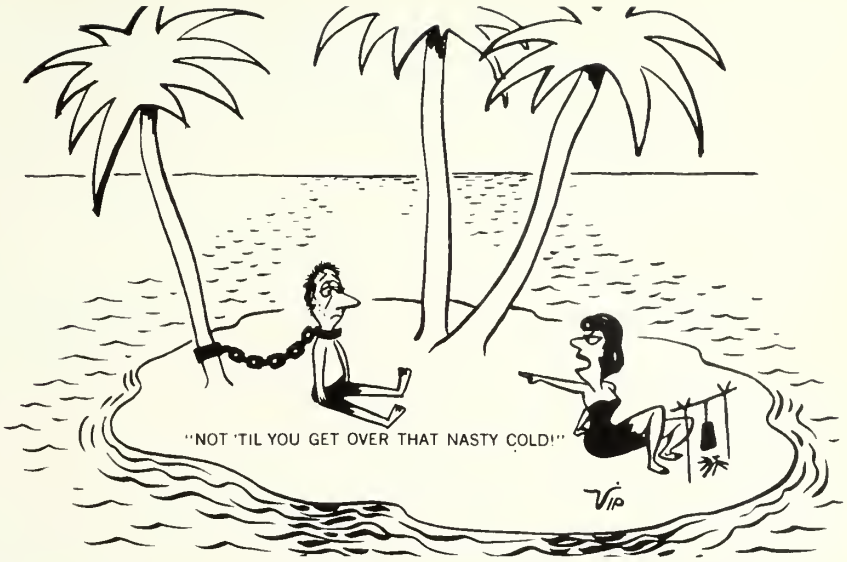
(Continued on Page 36)



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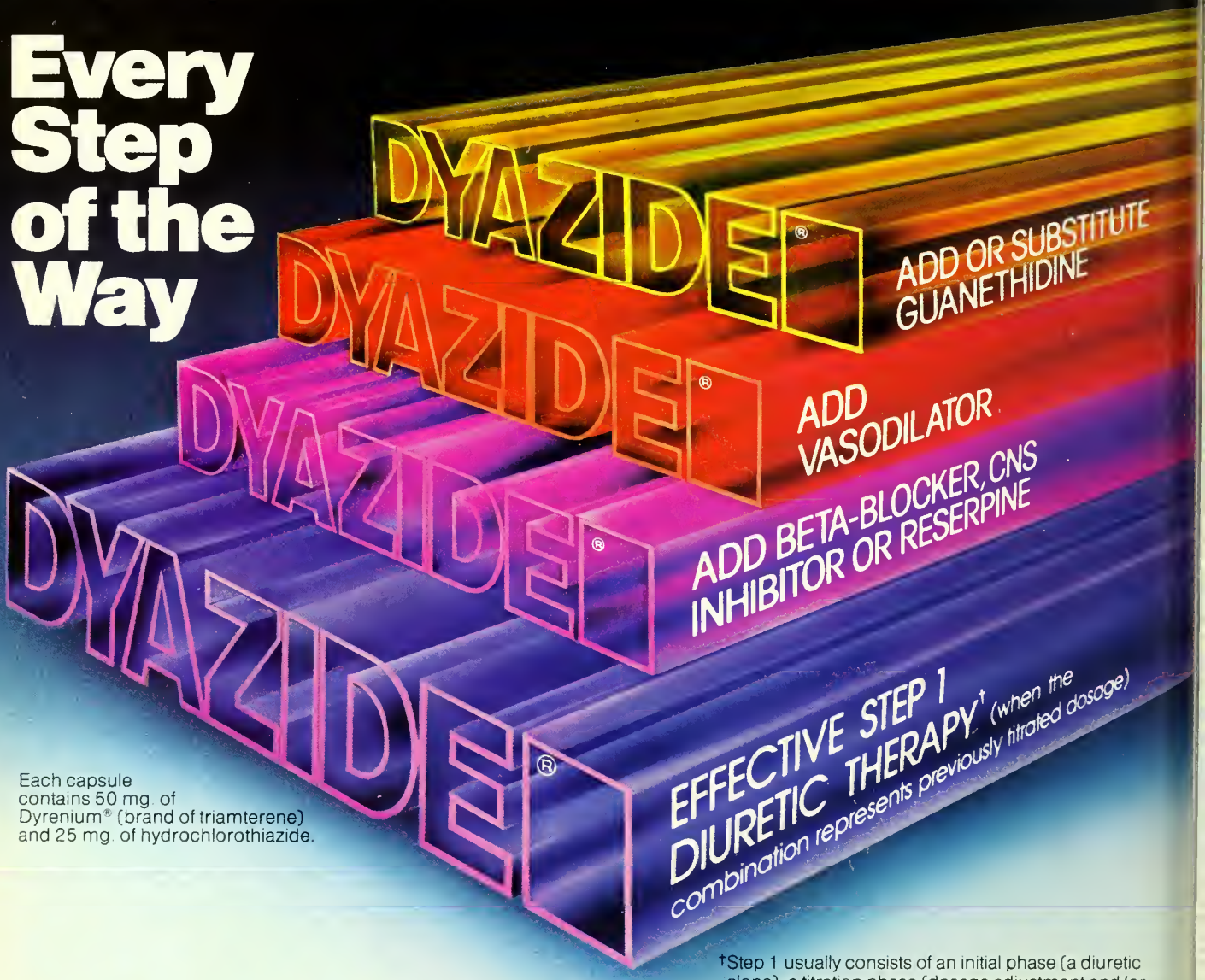

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently, both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

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JOHN C. BECK, MD

Introduction

THE ELDERY are a vulnerable group in our society —a group whose numbers are steadily growing. In 1953 life expectancy in the nation was 69 years; now it is 75 years; in 2003 it is projected to be 79 years, with a widening differential in life expectancy between men and women. Today, more than 11 percent of the US population—nearly 26 million Americans—are 65 and over, and this population is expected to exceed 55 million in the next 40 years. The most rapidly growing segment of our population is the over 75-year-old age group.

Although the elderly are consumers of extensive medical and social services, these services are generally not tailored to their needs. There is a perception by some that the elderly require a disproportionately large share of health and medical services, although there are others who would strongly suggest that they are not getting as much as they deserve. As health care spending for and by the elderly has increased, questions have been raised about the availability, quality and appropriateness of the health services they receive. Concerns like these have come to be known as the demographic or geriatric imperative. For the first time in the history of this nation, legislators and professions must address themselves to the graying of America. This poses a major challenge to the country's social, economic and health professional systems—the development of more effective care for older Americans.

Older persons are often the victims of multiple insults—physical, social and economic. Those who would care adequately for the elderly need the requisite skills to mobilize the variety of resources necessary to respond to this type of multifocal assault. The elderly often complain that they have difficulty finding physicians who are interested and specifically trained to care for them; and physicians and other health professionals, individually and collectively, must develop a strategy for responding to this expressed need.

In a 1977 American Medical Association survey of physicians, only 629 (0.2 percent) identified themselves in any way with geriatric care. Other studies indicate that physicians display a consistent pattern of minimal care to nursing home patients. The time that physicians spend with their patients, whether in an office or a hospital, decreases with the age of the patient regardless of the type of visit or the complexity of the problems. The reasons for these findings are complex but include the lack of specialized geriatric and gerontological training in the curricula of the medical educational continuum. Lack of attention to the elderly implies a real need for better understanding by the practicing profession of some of the special problems of these patients. These range from the basic biological, through the purely clinical, to the applied health services research area, and include the development of health policy. A special journal issue of this type cannot by its very nature cover the entire spectrum of concerns, but an attempt has been made to identify faculty in the medical schools of the western United States with particular interest and expertise in a diverse and comprehensive variety of topics. It is hoped that the information they present, widely disseminated, may begin to provide an improved understanding of the problems of the elderly and facilitate a better quality of medical care for them.

JOHN C. BECK, MD
Professor of Medicine and
Director
Multicampus Division of Geriatric Medicine
Department of Medicine
UCLA School of Medicine
Los Angeles

Age-Related Physiological Changes and Their Clinical Significance

GERRY R. BOSS, MD, *and* J. EDWIN SEEGMILLER, MD, *La Jolla, California*

Physiological changes occur with aging in all organ systems. The cardiac output decreases, blood pressure increases and arteriosclerosis develops. The lungs show impaired gas exchange, a decrease in vital capacity and slower expiratory flow rates. The creatinine clearance decreases with age although the serum creatinine level remains relatively constant due to a proportionate age-related decrease in creatinine production. Functional changes, largely related to altered motility patterns, occur in the gastrointestinal system with senescence, and atrophic gastritis and altered hepatic drug metabolism are common in the elderly. Progressive elevation of blood glucose occurs with age on a multifactorial basis and osteoporosis is frequently seen due to a linear decline in bone mass after the fourth decade. The epidermis of the skin atrophies with age and due to changes in collagen and elastin the skin loses its tone and elasticity. Lean body mass declines with age and this is primarily due to loss and atrophy of muscle cells. Degenerative changes occur in many joints and this, combined with the loss of muscle mass, inhibits elderly patients' locomotion. These changes with age have important practical implications for the clinical management of elderly patients: metabolism is altered, changes in response to commonly used drugs make different drug dosages necessary and there is need for rational preventive programs of diet and exercise in an effort to delay or reverse some of these changes.

NORMAL AGING affects all physiological processes. Subtle irreversible changes in the function of most organs can be shown to occur by the third and fourth decades of life, with progressive deterioration with age. The rapidity of the decline in function varies with the organ system under consideration but is relatively constant within a given system. Thus, the rate of aging is the same for a 45-year-old man as it is for an 85-year-old man; the difference is that by 85 years of age more age-related changes have accumulated. An important concept not widely appreciated is the distinction that must be made between the normal attrition of function occurring in all persons with advancing age and the loss of function that marks the onset

Refer to: Boss GR, Seegmiller JE: Age-related physiological changes and their clinical significance, *In* Geriatric Medicine. West J Med 135:434-440, Dec 1981

Dr. Boss is Assistant Professor of Medicine, Division of General Internal Medicine, Department of Medicine, and Dr. Seegmiller is Professor of Medicine and Chief, Arthritis Division, Department of Medicine, University of California, San Diego, School of Medicine, La Jolla, California.

Reprint requests to: Gerry R. Boss, MD, Department of Medicine, University Hospital, 225 Dickinson Street, San Diego, CA 92103.

of pathological changes from one or more of the diseases encountered with increased prevalence in the older age group. Failure to recognize this difference can lead to progressive disability from treatable diseases in many cases.

In this review we will discuss some of the physiological changes that occur with aging in the cardiovascular, respiratory, renal, gastrointestinal, endocrine, skin and musculoskeletal systems and their consequence for various therapeutic approaches in the day-to-day management of patients. We will concentrate mostly on changes that are of clinical importance and not discuss the increased incidence of such disorders as neoplasia that are well known to occur in all these systems. The attrition of the neurological and immune systems with age are discussed in other sections of this issue.

Cardiovascular System

Heart

Cardiac output decreases linearly after the third decade at a rate of about 1 percent per year in normal subjects otherwise free of cardiac disease.[1] Due to the small decrease in surface area with age the cardiac index falls at a slightly slower rate of 0.79 percent per year. The cardiac output of an 80-year-old subject is approximately half that of a 20-year-old. The basis of this decrease in cardiac function is unknown but may relate to one of several factors.

First, senescent cardiac muscle has a decreased inotropic response to catecholamines, both endogenous and exogenous, and, perhaps of more clinical significance is a decreased response to cardiac glycosides.[2] Second, with aging there is an associated increase in diastolic and systolic myocardial stiffness, perhaps due to increased interstitial fibrosis in the myocardium.[3] Third, there is a progressive stiffening of arteries with age, particularly of the thoracic aorta, leading to an increased afterload of the heart.[4] And finally, in autopsy studies as many as 78 percent of subjects older than 70 have been shown to have amyloid deposits in the myocardium, predominantly in the atria, but also in the ventricles and pulmonary vessels.[5] When amyloid is present in the ventricles and vessels it may lead to congestive failure, often with conduction defects. Cardiac amyloidosis may be a relative contraindication to treatment with digoxin since there appears to be an increased risk of arrhythmias.

Hypertension

A progressive increase in blood pressure after the first decade of life has long been regarded as a *normal* consequence of aging and was the basis for ignoring the presence of hypertension in the elderly. Only in the past decade or so have prospective studies provided evidence of the grave portents of hypertension for the older age group as well as the young and the potential preventive value of early treatment. The elevation with age is more pronounced for systolic than diastolic pressure. When hypertension is defined as a systolic blood pressure of greater than 160 mm of mercury and simultaneously a diastolic of greater than 95 mm of mercury, approximately 16 percent of the general adult population is hypertensive but about 50 percent of those over age 65 are hypertensive.

The Framingham Study clearly established that high blood pressure is a significant risk factor for stroke, coronary artery disease and congestive heart failure.[6] Moreover, cardiovascular disease was a more frequent cause of death and morbidity in the hypertensive subjects older than 65 years of age than in the younger subjects. More recently the Hypertension Detection and Follow-up Program confirmed these findings and showed, as did the Veterans Administration Cooperative Study, that treatment was beneficial.[7] All of these studies, as well as the European Working Party on High Blood Pressure in the Elderly, have shown that blood pressure in the elderly can be safely lowered when the antihypertensive therapy is chosen carefully and monitored regularly. The main question that needs to be answered at present is whether isolated systolic hypertension needs to be treated in elderly patients. Not enough data are yet available to answer this question and large-scale clinical trials are desperately needed. The discovery of nearly a dozen population isolates throughout the world among whom blood pressure does not increase with advancing age is provocative. In each isolate the culture had no access to added salt in the diet, suggesting an additional possible preventive approach that needs evaluation in our own culture.

Arteriosclerosis and Coronary Artery Disease

Thickening of the walls of arteries with hyperplasia of the intima, collagenization of the media and accumulation of calcium and phosphate in elastic fibers progressively occurs with aging. In addition, the lipid content of nonatherosclerotic

portions of vessels increases, particularly of cholesterol.[8] Although none of these age-related changes has definitely been shown to be a precursor of arteriosclerosis, atherosclerosis clearly increases with aging. Raised fibrous plaques that contain lipid, atheromas, of the abdominal aorta increase linearly from onset at about age 20 to reach approximately 30 percent by age 70. In general, atherosclerosis occurs earlier in the aorta and carotid arteries than in the coronary and cerebral arteries and peripheral vascular disease appears later. Myocardial infarction from coronary artery disease increases dramatically with age and although many risk factors are known, age itself is probably the most significant. Prevention at present is aimed at amelioration of the other factors, such as hypertension, obesity and cigarette smoking.

Respiratory System

Lung Volume

A linear decrease of vital capacity is found that amounts to a decrement of about 26 ml per year for men and 22 ml per year for women starting at age 20.[9] The total lung capacity remains constant, however, and thus the residual volume increases with age. The ratio of residual volume to total lung capacity (RV/TLC) is about 20 percent at age 20 and increases to 35 percent by age 60, with most of this increase in RV/TLC occurring after age 40.[10] In most studies the functional residual capacity also increases, although not as rapidly as the residual volume.

Gas Exchange

Although alveolar oxygen tension remains constant with age, arterial oxygen pressure shows a progressive decrease, thus increasing the alveolar-arterial oxygen difference $(A\text{-}a)O_2$.[9] Most of this decrease in arterial oxygen pressure results from a mismatch of ventilation and perfusion. The elastic recoil of the lungs decreases with age and thus there is a greater tendency for airways to collapse. This is measured as an increase in "closing volume" which increases linearly above the age of 20.[11] Airway closure occurs predominantly in the dependent zones of the lung and in the upright position this will result in a ventilation-perfusion mismatch because more perfusion occurs in the lower lobes. Although an age-related decrease in carbon monoxide diffusing capacity has been shown, it is unclear whether this contributes to the reduction in arterial oxygen pressure.

Flow Rates

There is a 20 percent to 30 percent decrease in maximum voluntary ventilation, forced expiratory volume in one second, maximal expiratory flow rate and maximum midexpiratory flow during adult life.[9] The basis for these changes is not known but again may relate to a decrease in the elastic recoil properties of the lung. This would result in both a decreased ability to generate normal expiratory pressures as well as increased resistance to expiration due to abnormally early airway collapse.

Infections

It is well known that elderly patients have a pronounced increase in incidence of pneumonia, both bacterial and viral, compared with younger persons. Although much of this may be due to a general depression of immune system function, other more specific factors may play a role. Pneumonia generally results from aspiration of oropharyngeal secretions and such aspiration appears more frequent in the elderly. Perhaps of even greater importance, the normal mechanical clearing of the tracheobronchial tree by the mucociliary apparatus is significantly slower in nonsmoking older persons than in their younger counterparts. Finally, due perhaps to poor oral hygiene, decreased flow of saliva or difficulty with swallowing, older persons have a higher rate of colonization of their oropharynx with Gram-negative bacilli than do younger persons.

Genitourinary System

Kidneys

A gradual decrease in the volume and weight of the kidneys occurs with aging so that by the ninth decade renal size is about 70 percent of that of the third decade. Moreover, there is a decline in the total number of glomeruli per kidney from about 1,000,000 below the age of 40 to about 700,000 by age 65.[12,13] With the reduction in the number of glomeruli there is a concomitant age-related decrease in the creatinine clearance (C_{cr}) and the decline is according to the following equation[14]:

$$C_{cr}\,(\text{ml/minute}) = 135.0 - 0.84 \times \text{age (years)}.$$

The serum creatinine concentration, however, changes little with age.[15] This is because of an age-related decrease in creatinine production due to a reduction in muscle cell mass that parallels the decrease in glomerular filtration rate.

This attrition in renal function has significant

consequences for the clinical management of elderly patients. Thus, drugs such as aminoglycosides, digoxin, penicillin and tetracycline which are primarily cleared by glomerular filtration will have a prolonged half-life in an elderly person even when the dosage is modified through the standard use of the serum creatinine concentration. In fact, in one study the half-life of these drugs in older subjects with a normal serum creatinine concentration was about twice that in younger persons.[16] Although the serum creatinine concentration does not change, there is a small but significant age-dependent increase in the blood urea nitrogen (BUN) concentration and the rate of rise is approximated by the following equation[17]:

$$\text{BUN (mg/dl)} = 7.56 + 0.119 \times \text{age}.$$

This increase in the blood urea concentration is not always seen, however, since there is frequently a decrease in the intake of protein as well.

Tubular function also declines with aging. The maximal reabsorption of glucose follows a linear decrease such that the glucose *threshold* ranges from 130 to 310 mg/dl in elderly persons. Glycosuria may therefore be misleading in the diagnosis and management of diabetes mellitus in older persons. Both the concentrating and diluting ability of the kidneys also slowly deteriorates. This may contribute to the increased proclivity for dehydration and hyponatremia seen in older patients although excessive use of diuretics probably plays a more major role. Interestingly, in the absence of congestive heart failure or urinary tract obstruction or infection, the nocturia of old age appears to be primarily of a central nonrenal origin due to a disturbance in the normal diurnal rhythm of excretion.[18]

Bladder

Urinary incontinence has been found in 17 percent of men and 23 percent of women older than 65 years.[19] In about half of the women and a fifth of the men this was due to stress incontinence alone. The capacity of the bladder decreases with age from about 500 to 600 ml for persons younger than 65 to 250 to 600 ml for those older than 65. Perhaps more important, in younger persons the sensation of needing to void occurs when the bladder is little more than half filled but in many who are older the sensation occurs much later or sometimes not at all, leading to overflow incontinence. These changes appear to be due more often to central nervous system disease than to bladder dysfunction.

Prostate

Enlargement of the prostate occurs in most older men; by age 80 more than 90 percent of men have symptomatic prostatic hyperplasia with varying degrees of bladder neck obstruction and urinary retention. Prostate surgery is required in 5 percent to 10 percent of all men at some time. Recently the cause of the hyperplasia has been more clearly defined; the concentration of dihydrotestosterone (DHT) increases in prostatic cells.[20] The increase in the intraprostatic concentration of DHT is due to two age-related changes: an estrogen-mediated enhancement of androgen receptors on prostatic cells as well as a decrease in the intracellular catabolism of DHT. Future treatment of benign prostatic hyperplasia may be endocrinologic, aimed at reducing the intracellular concentration of DHT by competitive steroid antagonists.

Gastrointestinal System

Esophagus

Age-related changes of esophageal function, so-called presbyesophagus, are due primarily to disturbances of esophageal motility. The esophagus in an older person may have a decreased peristaltic response, an increased nonperistaltic response, a delayed transit time or a decreased relaxation of the lower sphincter on swallowing. The decrease in peristalsis and delay in transit time may lead to dysphagia with a voluntary curtailment of caloric consumption. Nonperistaltic contractions are found almost exclusively in the elderly. They occur in the lower two thirds of the esophagus and are the cause of the "corkscrew" esophagus seen on barium swallow studies. Decreased relaxation of the lower esophageal sphincter on swallowing is the basis of achalasia and is more common in the elderly population.

Stomach

The incidence of atrophic gastritis increases significantly with age. In a Scandinavian study approximately 40 percent of apparently healthy subjects older than 65 had evidence of atrophic gastritis.[21] At present, atrophic gastritis is divided into type A which is confined to the body and fundus sparing the antrum and type B which is associated with atrophy of both antral and fundic

glands. Both types increase in frequency with advancing years. Severe atrophic gastritis results in achlorhydria, deficient intrinsic factor secretion, decreased pepsinogen production and, in type A, hypergastrinemia due to lack of acid inhibition of gastrin cell secretion. Type A atrophic gastritis appears to be an autoimmune disease, whereas type B may be due to local environmental factors such as chronic enterogastric bile reflux. Both types of atrophic gastritis are premalignant lesions.

Colon

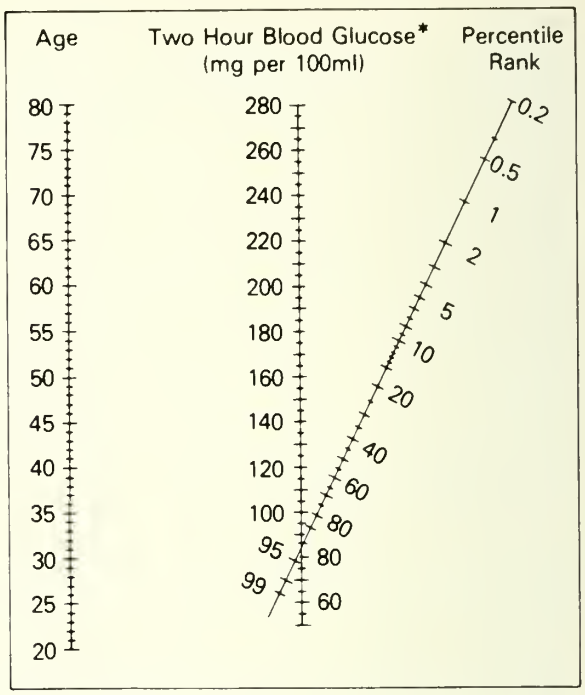
A decrease in intestinal motility occurs with age. The colon becomes hypotonic, which leads to increased storage capacity, longer stool transit time and greater stool dehydration. These are all etiologic factors in the chronic constipation that plagues the aged. Laxative abuse therefore results and is the most common cause of diarrhea in the elderly. A high-fiber diet is the treatment of choice and this can best be achieved by prescribing a diet rich in bran. Whether or not constipation is an etiologic factor in diverticulosis remains unclear but age certainly is. Diverticula are uncommon below the age of 40 but steadily increase thereafter until nearly 50 percent of those older than 80 have diverticulosis. Symptoms are present in only about 20 percent to 25 percent of those who are affected and severe disease with inflammation and bleeding occurs in a much smaller number.[22]

Sphincter Control

Loss of control of the internal and external anal sphincters in the elderly in the presence of essentially normal cognitive function is a most emotionally traumatic and demeaning experience. The resulting fecal incontinence is one of the major causes for admission of many otherwise healthy persons to long-term care facilities. Recent studies have shown the cause to be a loss of tone of the external rectal sphincter. Biofeedback techniques allowed the regaining of sphincter and bowel control in as many as 70 percent of a group of patients studied.[23]

Liver and Biliary Tract

The liver decreases in weight by as much as 20 percent after the age of 50 but perhaps because of its large reserve capacity this attrition is not reflected by a decrease in the usual liver function tests. Although tests of liver function show little or no change with age, a large number of drugs such as diazepam and antipyrine are known to



* The oral glucose dose was 1.75g per kilogram (kg) of body weight

Figure 1.—Nomogram for correcting the glucose tolerance test for age. (Reproduced from Andres[21] with permission of publisher and author.)

be metabolized more slowly by the liver in the elderly. This alteration in hepatic drug metabolism may be due to a decrease in the appearance, amount or distribution of the smooth endoplasmic reticulum. Biliary tract disease is unusual before the third decade and the incidence of cholelithiasis increases greatly with age. In a large autopsy series of subjects older than 70 years, 30 percent had gallstones and another 5 percent had previously had a cholecystectomy. In general, surgical operation is indicated in patients with gallstones, even if asymptomatic, since the risk of complications in an elderly patient is greater than the risk of operation.

Endocrine System

Glucose Homeostasis

Increasing age results in a progressive deterioration in the number and the function of insulin-producing beta cells.[24] The capacity of these cells to recognize and respond to changes in glucose concentration is impaired. In elderly subjects a greater proportion of the insulin released into the circulation in response to a glucose challenge is in the form of the inactive precursor proinsulin than in their younger counterparts. Of perhaps even

greater importance is the development of progressive peripheral insulin resistance with age. Compared with younger persons the elderly have a relative decrease in lean body mass with a relative increase in adiposity. Since little change in the total number of fat cells occurs with age, the increased adiposity appears due to an increase in fat cell size. In general, as adipocytes enlarge they turn down their insulin receptors. Thus, even in nonobese elderly persons there is peripheral insulin resistance due to increased size of adipocytes with a relative decrease in insulin receptors. The combination of abnormal beta cell function with peripheral insulin resistance leads to increased glucose intolerance in normal aged persons.[25] Figure 1 is a nomogram for correcting the glucose tolerance test for the age of the patient, an important consideration in the diagnosis of diabetes in the elderly.[24]

Although diabetic ketoacidosis and lactic acidosis are uncommon in elderly diabetic persons, hyperosmolar nonketotic coma occurs with some frequency.[26] As already discussed, there is a decrease in the renal concentrating function with age as well as a decrease in the maximal reabsorption of glucose. Thus, even mild hyperglycemia may lead to osmotic diuresis. This will cause further hyperglycemia and ultimately dehydration. The dehydration may lead to vascular insufficiency in elderly patients and they may become obtunded and refuse to drink; rapid progression to coma may then ensue. This syndrome is frequently precipitated or exacerbated by a myocardial infarction, pneumonia or urinary tract infection.

Osteoporosis

Osteoporosis is a skeletal disorder characterized by a decrease in bone mass which may result in mechanical failure of the skeleton. The decrease in bone mass is an age-related phenomenon. Beginning in the fourth decade there is a linear decline in bone mass at a rate of about 10 percent per decade for women and 5 percent per decade for men. Thus, by the eighth and ninth decades 30 percent to 50 percent of the skeletal mass may be lost. The decrease in bone mass is due to a relative increase of bone resorption over formation but the basis of this is unknown. Hormonal factors certainly play a role since women are more susceptible than men and the rate of development of osteoporosis in women accelerates after menopause. Moreover, low-dose estrogen therapy can arrest or retard bone loss if begun shortly after the menopause.[27,28]

Menopause

Nowhere are the development of age-related changes more apparent than in the human female climacteric. Menopause occurs because of the disappearance of oocytes from the ovary through ovulation and atresia. Little is understood about the process of ovarian atresia and whether it is due to primary ovarian failure or secondary to hypothalamic-pituitary changes.

Several consequences of the menopause deserve mention. First is the vasomotor instability or hot flashes. Two thirds to three quarters of menopausal women will experience flushing, with 80 percent having the symptoms for longer than one year and 25 percent to 50 percent for more than five years. Changes in skin temperature, skin resistance, core temperature and pulse rate occur during the flush. Besides being a major disturbance while women are awake, the hot flashes may occur during sleep, leading to waking episodes. Insomnia with possible physiologic and psychologic disturbances may thus result.

It is well known that arteriosclerotic cardiovascular disease is unusual in women before the menopause. The precise protective mechanism of ovarian function is not known, but premenopausal women have a higher ratio of high-density lipoproteins to low-density lipoproteins than do postmenopausal women. Osteoporosis with its relation to the menopause has already been discussed. Changes of the skin occur with age and the recent demonstration of estrogen receptors in the skin of mice suggests that estrogens could have direct effects on aging of the skin (see below).

Skin

Epidermis

Atrophy of the epidermis occurs with age and is most pronounced in exposed areas: face, neck, upper part of the chest, and extensor surface of the hands and forearms. In addition to the thinning of the epidermis there is notable flattening of the dermal epidermal junction with effacement of both the dermal papillae and the epidermal reti pegs. The turnover rate of cells in the stratum corneum decreases with age and in persons older than 65 it takes 50 percent longer to reepithelialize blistered skin than in young adults. The

decrease in epidermal cell growth and division causally contribute to the increased incidence of decubitus ulcers in older patients.[29]

Dermis

Dermal collagen becomes stiffer and less pliable with age; elastin is more cross-linked and has a higher degree of calcification. These changes cause the skin to lose its tone and elasticity, resulting in sagging and wrinkling.[30] An age-related decrease in the number of dermal blood vessels also develops. This relative ischemia of the skin may also play a pathogenetic role in the development of decubitus ulcers.

Musculoskeletal System

Muscle

The age-dependent decline in lean body mass is well known and is primarily due to loss and atrophy of muscle cells. Some muscles, such as the diaphragm, show few if any changes while others, such as the soleus, show pronounced infiltration by collagen and fat.[31] Age-related changes also occur in the innervation of muscle but the exact pathologic process is not well understood. Although much of the decreased locomotion of elderly subjects is due to skeletal changes (see below), a substantial part is probably secondary to decreased muscle mass and function.

Skeletal

Degenerative joint disease occurs in 85 percent of persons older than 70 years of age and is a major cause of disability. It affects both the peripheral and axial skeleton and is characterized by degeneration of cartilage, subchondral bone thickening and eburnation, and remodeling of bone with formation of marginal spurs and subarticular bone cysts. Due to its predilection for weight-bearing joints, wear-and-tear type mechanisms must be operative. When the degenerative changes are pronounced, pain can be severe, greatly limiting the activity status of an elderly patient. Fortunately, adequate drug and surgical treatments exist but old people are truly restricted by their joints.

Conclusion

We have briefly discussed some of the major changes that occur with age in several of the body systems. Although it is tempting to regard many of the so-called diseases of the elderly as being the end stage of normal physiologic changes that occur with aging, a distinction between the attrition in function of normal aging and pathological states must be clearly delineated. To do otherwise jeopardizes a patient's prospect for receiving preventive and remedial therapy.

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Important Infections in Elderly Persons

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Elderly persons are prone to more frequent or greater morbidity and higher mortality from selected infectious diseases than the average population. Factors that may affect this increased predilection or poorer prognosis include environmental exposure, normal physiological changes of aging, coexistence of chronic diseases and alteration of host defense mechanisms.

Infections to which the aged are particularly vulnerable are pneumonia, influenza, tuberculosis, urinary tract infection, Gram-negative bacteremia, intra-abdominal sepsis, soft tissue infection, infective endocarditis, bacterial meningitis, bacterial arthritis and herpes zoster infection.

MOST CLINICIANS ACCEPT the view that elderly persons are more prone to acquire infectious diseases compared with the general population. However, there are only limited data that clearly validate this concept. Available information suggests that the elderly may be highly vulnerable to selected infections and not necessarily to all types of infectious diseases.[1] We review those infections that are particularly important to the aged.

Risk Factors for Infection in the Aged

Although aberrations of host defense mechanisms with aging are thought to be the major risk factors for acquiring infection, other general factors may be equally important.[2]

Environmental Exposure

For an infection to develop, the host must be exposed to microbes either endogenously or exogenously. With the increase in average life span for both men and women, the elderly are afflicted with more chronic illness, requiring more time in hospital. Patients 65 years or older are responsible for approximately a third of all days spent in hospital in the United States.[3] In general, the average risk of acquiring a nosocomial (hospital-acquired) infection is approximately 4 percent.[4] However, the elderly have a relative risk rate for nosocomial infection that is nearly three times that of the general population.[5] One explanation may be that admittance of older persons to hospitals or institutions results in a high incidence of pharyngeal colonization with Gram-negative bacilli.[6] Indeed, a half to two thirds of nosocomial infections are caused by Gram-negative bacilli.[7] Other kinds of nosocomial infections that the aged are susceptible to include *Staphylococcus aureus, Candida* sp, herpesvirus group and influenza virus, and *Pneumocystis carinii*.[8]

Physiological Changes With Aging

There is a general decline in organ function with aging. A perplexing issue in gerontology and geriatrics is to determine whether a change is strictly ascribable to age alone, independent of environment or disease processes. It is not within the scope of this discussion to review the physiological changes that occur with aging. (These

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changes are discussed extensively by Boss and Seegmiller elsewhere in this issue.) However, age-associated changes in organ structure and function do occur,[9] and many of these alterations may contribute to the increased risk of infection in the elderly.

Diseases That Increase Susceptibility to Infection

The incidence of a variety of malignant conditions increases with age. These types of cancer often involve the stomach, breast, pancreas, lung or prostate.[10] Multiple myeloma and chronic lymphocytic leukemia also occur more frequently in the older population. In general, these diseases are associated with a higher incidence of infection.[11,12] Diabetes mellitus is a common disorder of the aged.[13] Selected types of infections (for example, urinary tract or soft tissue infections; malignant external otitis and osteomyelitis) appear more often in diabetic patients.[14] Prostatic hypertrophy in elderly men is a common cause of obstructive uropathy and, hence, urinary tract infection.

Alterations of Host Defense Mechanisms

Host defense mechanisms can be broadly categorized into four areas: mechanical factors, phagocytic activity, immunological mechanisms and complement activity. Mechanical barriers (such as skin and mucous membranes) are the first line of defense against microbial invasion. Skin changes with aging (such as thinning of epidermis, decreased glandular secretions and arteriosclerosis) and increased trauma, injuries and pressure sores in older persons result in more infections of skin and soft tissues. Mucosal changes such as those caused by cancer of the colon or diverticulosis can lead to intra-abdominal infections.

Phagocytic function of polymorphonuclear leukocytes appears to be normal in elderly persons.[15] Studies on macrophage phagocytosis in the aged are limited, but it appears that this function does not change significantly with advancing years.[2]

Humoral immunity abnormalities with aging have been less well defined than cell-mediated immunity. In part, this is due to differences in experimental design, whether animals or humans are studied, or whether immunoglobulin activity or B lymphocyte (B cell) function is assessed. It appears that serum levels of IgG and IgA immunoglobulins are unchanged, but IgM may be slightly decreased in the elderly.[15] Antibody response to vaccines is lower in older persons than in the young for both influenza and pneumococcal vaccines.[16,17] Total number of circulating B cells are unchanged with age, but there is evidence that regulatory T lymphocytes (T cells), such as suppressor and helper T cells, may play an important role in B cell responses to certain antigens such as pneumococcal polysaccharide.[18] There is also evidence that shows that aging may affect T cells that regulate antibody response but not necessarily the antigen-specific B cells.[19] Cell-mediated immunity declines with aging. Cell loss, shifts in the proportion of cell subpopulations and quantitative cellular changes are operative mechanisms.[19] These changes parallel the gradual involution and loss of the thymus with advancing years. Age-related decrement in cell-mediated immunity is illustrated by the diminution of a variety of T cell reactions and delayed hypersensitivity in elderly persons.[20]

Studies on complement in the elderly have been incomplete, but available information suggests no diminution in complement activity in this population.[15,21]

Important Infections in the Aged

It could be argued that if the elderly are more predisposed to infections, all infectious diseases are important. However, as mentioned earlier, limited clinical studies have identified only certain infections to be either more common or more devastating in older persons. The discussion below focuses on these selected infections.

Bacterial Pneumonia and Influenza

Pneumonia and influenza are still among the leading causes of death for persons 75 years or older in the United States. The incidence of influenza does not necessarily increase with age, but the death rates are higher in adults, especially in those beyond the age of 65 years.[22,23] *Streptococcus pneumoniae* is the most common pathogen isolated in elderly patients with community-acquired pneumonia. Bacteremic pneumococcal pneumonia in persons older than 70 has a death rate greater than 50 percent.[24] Gram-negative bacillary pneumonia in the elderly is increasing in incidence, both in acute care settings and in nursing homes.[25,26] It appears that oropharyngeal colonization with Gram-negative bacilli plays an important role in predisposition of aged patients to certain infections.[6] Recently, one report indicated that community-acquired Gram-negative

bacillary pneumonia occurred with the greatest frequency among the elderly.[27]

Tuberculosis

In the United States the incidence of tuberculosis in the elderly has decreased more slowly than in other age groups, resulting in the relative rate of this infection being highest in those 65 years or older.[28] In such patients, infection with *Mycobacterium tuberculosis* is a reactivation of primary disease acquired many years earlier. Tuberculosis may account for 15 percent of all geriatric pulmonary infections.[29] Moreover, an outbreak among elderly residents of a nursing home has been recently reported.[30] The failure to administer isoniazid chemoprophylaxis to the elderly (because of potential hepatotoxicity), disturbances of cell-mediated immunity, poor nutrition or other unknown factors may account for the high incidence of tuberculosis in this population.

Urinary Tract Infection

Urinary tract infection (UTI) is clearly widespread in the elderly population. Depending on residential status or the presence of an underlying disease, the incidence of UTI in men and women can range from 5 percent to 35 percent and 15 percent to 50 percent, respectively.[31] Prostatic hypertrophy, previous genitourinary instrumentation, poor emptying of the urinary bladder and perineal contamination from fecal incontinence are possible reasons for this high incidence.[32,33] The vast majority of cases of UTI in elderly patients are asymptomatic. However, bacteremia commonly results from UTI and can be devastating in the aged (see next section on Gram-negative bacteremia). Moreover, asymptomatic bacteriuria appears to shorten survival in otherwise healthy elderly persons when compared with those without bacteriuria.[34]

Gram-negative Bacteremia

Gram-negative bacteremia is generally a consequence of some primary focus of infection. Recent studies suggest that Gram-negative bacteremia occurs most often (age-specific attack rate) in patients older than 60 years.[35] Bacteremia associated with shock complicates older patients more frequently than younger adults.[36] Moreover, when shock intervenes, mortality may exceed 70 percent.[37] The relative importance of greater exposure to Gram-negative organisms (more days in hospital), alteration of host defense mechanisms to Gram-negative bacteria and diminution of physiological reserve (hemodynamically) to bacteremia in the elderly in explaining the observed high mortality is not yet clear.

Intra-abdominal Sepsis

For selected abdominal infections, intra-abdominal sepsis is of special importance to the elderly. These infections are appendicitis, diverticulitis and biliary sepsis. Although appendicitis is correctly thought of as a disease of the young, the aged do contract this disorder. Moreover, for a variety of reasons, morbidity and mortality are inordinately high in the old compared with the young. The mortality may be several times that of the general population[38] or as high as 20 percent in patients 60 years or older.[39] Similarly, complications like perforation, wound infection, abscess formation and pneumonia are more common in the elderly following appendectomies.

The risk of developing diverticulosis rapidly increases with aging.[40] In some 20 percent to 25 percent of all patients with diverticulosis, diverticultitis will develop.[41] Both diverticulitis and appendicitis may present as or be complicated by peritonitis if perforation accompanies these infections.

Cholelithiasis is another disease of the aged. Complications such as cholangitis, perforation, gangrene and development of common duct stones are more common in the elderly.[41] With each increasing decade, there is a higher incidence of biliary sepsis; more than 50 percent of patients 70 years or older—compared with 20 percent in younger persons—have bacteria isolated in the bile following cholecystectomy.[42] Other studies have shown the incidence of empyema and gangrene and the mortality for cholecystitis to be higher in patients 65 years or older.[43]

Soft Tissue Infections

Skin and soft tissue (wound) infection is a common complication in aged patients having operations, particularly procedures involving the abdomen. With the normal process of aging, the skin's defense mechanisms against infection are compromised. Under these circumstances, even minor trauma (common in the old) to the skin can result in serious skin and soft tissue infections.

Elderly persons are prone to the development of diabetic peripheral vascular disease. Infected foot ulcers (anaerobic and aerobic bacteria) asso-

ciated with diabetes are common ocurrences in the geriatric population.[44] Decubitus ulcers or pressure sores are predominantly a problem of the aged because of immobilization as a consequence of cerebral vascular accidents or other chronic debilitating diseases. Bacteremia with anaerobic and aerobic organisms from decubitus ulcers is not uncommon in patients older than 60 years, and mortality is extremely high.[45]

Infective Endocarditis

Over the past 35 years, there has been a change in age distribution for cases of infective endocarditis. As many as 30 percent of patients with infective endocarditis may be 60 years or older,[46] and in those with natural valve or prosthetic valve infection, the mean age may be 55 years.[47] Diagnosis is often difficult because a third of these elderly patients may not have a detectable murmur or underlying valvular disease.[48,49] Mortality associated with infective endocarditis increases with age[50] and may exceed 70 percent.[48]

Bacterial Meningitis

The most common causes of bacterial meningitis in elderly patients are pneumococci, Gram-negative bacilli and *Listeria monocytogenes*. More importantly, bacterial meningitis in this population is associated with exceedingly high mortality.[51-53] Pneumococcal meningitis in patients 70 years or older may result in a death rate of more than 80 percent. A recent study showed that aged patients with *L monocytogenes, Escherichia coli* and *Klebsiella* sp meningitis had death rates of 83 percent, 96 percent and 100 percent, respectively.[54]

Clinical findings of bacterial meningitis in the aged should be typical.[55] However, occasionally patients may present clinically with altered sensorium, dementia, or possible stroke without classic findings of meningitis. Moreover, elderly patients may have restricted neck mobility or nuchal rigidity resulting from cervical osteoarthritis, which may then dissuade a clinician from making the correct diagnosis of meningitis.

Bacterial Arthritis

Bacterial arthritis (excluding gonococcal arthritis) appears to have a predilection for developing in elderly patients.[56,57] Presence of underlying disease (for example, diabetes mellitus, cancer or cirrhosis) and previous joint damage (osteoarthritis, rheumatoid arthritis, gout, pseudogout and trauma) appear to be important factors in predisposing the old to bacterial joint infections.[58,59] The most frequent pathogen isolated is *Staphylococcus aureus*. However, there are reports now suggesting that Gram-negative bacillary arthritis may be increasing in the geriatric population. Goldenberg and co-workers[58] reported on 13 cases of arthritis caused by Gram-negative bacilli; 6 of the 13 patients involved were 60 years or older.

Herpes Zoster Infection

Herpes zoster infection (shingles) is a result of reactivation of the varicella-zoster virus that remained latent following an initial infection with varicella. Contrary to earlier teachings, most patients with zoster infection are otherwise healthy. This includes elderly persons. More than 45 percent of cases of zoster infection occur in those 60 years or older (70 percent are 50 years or older).[60] Additionally, postherpetic neuralgia primarily afflicts the elderly (20 percent to 40 percent of those more than 60 years of age with zoster).[61] Although it appears that antibody (passive immunization) in high titer can prevent or modify zoster infections in an exposed, susceptible person, it seems more likely that integrity of cell-mediated immunity rather than persistence of varicella-zoster antibodies is important in preventing disease.[61]

Summary

Elderly persons appear to be prone to more frequent or serious morbidity and higher mortality from infectious diseases than the general population. Available data suggest, however, that the aged may be highly vulnerable only to certain infections and not necessarily to all types of infectious disease. It is important that clinicians be aware of these selected diseases as well as the risk factors for infection in this older population.

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Hematologic Disorders in the Elderly

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Management of hematologic disorders in older patients must often be weighed in a setting of decreased physiological reserves and concurrent illnesses. Anemia in the elderly should never be attributed to old age. Even a mild anemia in collusion with multiple physical and mental problems may tip the balance for those previously able to cope with their disabilities. Iron deficiency anemia and the anemia of chronic disease are the most common types of anemia in the elderly. Nutritional anemias due to folate or vitamin B_{12} deficiency are treatable and should not be overlooked. Newer chemotherapy regimens for acute nonlymphocytic leukemia have been effective in many older patients. Decisions to treat are sometimes difficult, often depending on the aggregate of coexistent physical and mental disorders. The most prevalent type of leukemia in the elderly is chronic lymphocytic leukemia. A benign asymptomatic course requires no therapy, but aggressive disease requires treatment. Multiple myeloma should be suspected in an elderly person who has both unexplained anemia and bone pain. After definitive diagnosis, phlebotomy therapy should be considered for both polycythemia vera and secondary erythrocytosis to reduce blood viscosity and increase cerebral blood flow.

An overview of the effects of blood disorders in the elderly and a discussion of hematologic diseases that are more prevalent in the aged require brevity and selectivity. Anemia is common and has profound effects in the elderly and, therefore, will receive greater emphasis. Because of the increasing array of diagnostic and therapeutic modalities, a practical approach should be helpful to clinicians.

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Anemia in the Elderly

In active, healthy, elderly people, blood problems develop similar to those of younger adults, and such persons have essentially the same response to treatment. Aging, however, reduces physiological reserve capacity, which often decreases tolerance to physical activity and slows the rate at which many body functions return to normal following stress. In an older person, therefore, an anemia may produce a disability far beyond that expected. Unfortunately, increased weakness, fatigue and a mild anemia is easily attributed to old age. Society, physicians and older people themselves often view illness and

ABBREVIATIONS USED IN TEXT

CLL = chronic lymphocytic leukemia
TIBC = total iron-binding capacity

disability as an ordinary consequence of aging. Older people tend to minimize their problems and the statement is often heard, "It's just old age." Furthermore, as people get older they acquire more diseases. Geriatric patients are distinguished by multiple, interacting disorders that produce disability that is more than just additive. Multiple disorders requiring use of numerous drugs with attendant risks of adverse effects frequently modify or confuse the clinical picture. Furthermore, nutritional deficiencies should always be of concern in the elderly. An older person may have nutritional anemia from underlying disease, dementia, depression, alcohol, drugs or deprivation due to lower income or living alone.

There is no such entity as anemia of old age. Old people are anemic because they have disease. Anemia is often a presenting sign of a serious underlying disease and must be considered such at any age. There is disagreement about normal hemoglobin levels in the elderly.[1-4] On the one hand, it is reported that there is no change from normal adult values while other reports indicate a 1 to 2 grams per dl reduction, especially in men. Better studies of active, healthy, elderly men and women in each decade of life are needed to establish normal values. Old people with even mild anemia are entitled to the same consideration for diagnostic studies as younger adults; otherwise, treatable anemia and its associated underlying disease will go undetected.

Signs and symptoms of anemia may appear at higher hemoglobin levels in the elderly. Even mild to moderate anemia may produce confusional states or worsen an existing dementia. An elderly person may be wrongly branded with a diagnosis of dementia on the basis of behavioral changes produced by anemia. In elderly patients with coronary artery disease, ischemic chest pain or congestive heart failure may develop. Syncope and falls may occur with anemia as a result of postural hypotension and weakness. Exertional dyspnea may be due to anemia, concomitant chronic pulmonary or cardiac diseases.

Anemia itself is not a diagnosis but a sign of disease. Successful management of anemia is dependent on an accurate diagnosis. Anemia in the elderly is often due to multiple causes. Iron deficiency anemia and the anemia of chronic disease are the most common types that occur in the elderly. Nutritional anemias resulting from folate or vitamin B_{12} deficiency are treatable and should not be overlooked.

Iron Deficiency

Iron deficiency is the most common cause of reduced hemoglobin synthesis. Symptoms of iron deficiency are related not only to a diminished oxygen transfer to tissues because of less hemoglobin, but to iron deficiency itself.[5,6] The physician, therefore, often sees significant improvement in physicial activity after treatment with iron before an increase in hemoglobin concentration.[5,6] Because of the profound effects that a minimal decrease in hemoglobin concentration can have on other disabilities in the elderly patient, therapy should never be withheld because of the belief that a small increase in hemoglobin will be of little consequence. Physicians may be surprised by unexpected improvement with successful treatment even in patients with mild anemia.

Severe iron deficiency anemia is characterized by hypochromia, low reticulocyte index, hypoferremia, an increase in total iron-binding capacity (TIBC), low transferrin saturation, absent bone marrow iron and an increase in free erythrocyte protoporphyrin. However, in mild degrees of iron deficiency, the erythrocyte morphology and indices may be normal. In such circumstances, low serum iron levels associated with an elevated TIBC indicate iron deficiency. However, in the elderly with multiple underlying diseases, transferrin is reduced and the TIBC is low or normal in many patients with iron deficiency. In this situation, an abnormally low serum ferritin value establishes the diagnosis. The serum ferritin level is a good indicator of the amount of stored iron and can be substituted for bone marrow assessment of iron stores.[7,8] This test is now becoming universally available, is a reliable and sensitive indicator of iron deficiency, and will be increasingly used because of some limitations of the TIBC in the elderly. In patients with iron deficiency anemia, the serum ferritin levels are below 12 μg per liter. There is less confusion in interpretation of serum ferritin levels in elderly women because the concentration rises sharply in postmenopausal women as well as progressively in aging men.[9,10] Serum ferritin levels must be interpreted with

knowledge of the clinical condition. When iron deficiency and inflammatory disease coexist, the serum ferritin concentration is higher and a value below 25 μg per liter would suggest iron deficiency. Similarly, a value below 100 μg per liter in a patient with liver disease and below 50 μg per liter in a hemodialysis patient, suggests iron deficiency.[7,11,12]

Clinical judgment determines the number and sequence of tests done just as in the younger population. Hypochromia in a patient with chronic bleeding indicates iron deficiency anemia. If there is no obvious bleeding and stool specimens are negative for occult blood, a low serum iron level associated with an increased TIBC or diminished serum ferritin indicates iron deficiency anemia.

Management implies not only treatment of iron deficiency but also the identification and, if possible, correction of the abnormality causing the anemia. Poor nutrition may be a contributing cause of iron deficiency, although it is seldom the sole cause. Iron excretion in the elderly is limited to approximately 1 mg daily, thereby requiring up to three years to exhaust iron stores before anemia develops. Nonetheless, dietary problems in the elderly should be carefully assessed. The amount of dietary iron is closely related to caloric intake, which is usually about 6 mg of elemental iron per 1,000 calories. Iron from animal tissue is better absorbed than iron in vegetables. Vegetable sources may be high in iron content, but the iron is poorly absorbed unless consumed with meat, because of inhibitors of its absorption. Tea also inhibits iron absorption.[13] Some elderly people drink large amounts of tea daily, which may become a contributing factor in iron deficiency, especially if the diet consists mainly of vegetables.

Clinicians should never attribute iron deficiency to a poor diet until investigation for a bleeding lesion has been completed. Testing for occult blood in the stool is an essential part of the examination of every patient. Bleeding may be intermittent and, therefore, even if tests for occult blood are negative, a thorough search for a gastrointestinal lesion is still warranted. Gastrointestinal bleeding in older people may be due to drugs, including aspirin, phenylbutazone, indomethacin, steroids, alcohol and intravenously given ethacrynic acid.[14] Although a patient has been ingesting these drugs, it is unwise to ascribe gastrointestinal bleeding to them until other gastrointestinal lesions are excluded.[15] Prominent causes of gastrointestinal bleeding are peptic ulcer, gastritis, esophageal varices, hiatal hernia, colonic diverticula, polyps, carcinoma and vascular ectasias. Vascular ectasias of the cecum and ascending colon are increasingly recognized as a cause of bleeding in patients 60 years or older.[16] Diverticulosis, even in the absence of diverticulitis, is a prominent cause of bleeding, especially right-sided colonic diverticula.[17] Elderly patients lived in an era when partial gastrectomy was in vogue for treatment of peptic ulcer. Iron deficiency anemia resulting from dietary deficiency, malabsorption or blood loss is a subsequent common problem, with an incidence of 50 percent up to ten or more years after operation.[18]

Replacement of iron by daily oral administration of two to four tablets of ferrous sulfate, depending on the severity of the anemia, produces an elevation of hemoglobin after ten days, with a normal value reached within six weeks. After correction of the anemia, the amount of iron absorbed diminishes and therapy must be continued for at least an additional four months to replenish bone marrow iron stores. There is no difference in iron absorption in young or old patients with iron deficiency.[19] Failure of adequate iron therapy to improve hemoglobin concentration in an elderly patient is usually a result of noncompliance, incorrect diagnosis or continued bleeding. Poor absorption may occur with slow-release iron preparations, concomitant use of antacids, tea, eggs, or bran in cereals and bread ingested with iron tablets. Poor compliance is an important barrier to effective therapy in elderly patients. Older people with multiple diseases who are taking several medications require a simple, uncomplicated drug regimen. A recent study suggests that an iron tablet containing 105 mg of elemental iron taken once a day is effective in elderly iron-deficient patients.[20]

Parenteral therapy with iron dextran (Imferon) is indicated for unreliable patients who will not comply with oral therapy, are intolerant of iron given by mouth or are unable to absorb the iron because of gastrointestinal disease or an operation. Iron dextran may be administered either intramuscularly or intravenously. With the former, a test dose of 0.25 ml is injected the first day followed by 2.5 ml in each buttock intramuscularly until the calculated dose has been given. In patients with small muscle mass or hemorrhagic disorders, iron dextran may be infused intravenously by either an intermittent or total-dose infusion method. With the intermittent

intravenous method, a test dose of 0.5 ml (25 mg) is given the first day followed by daily intravenous injections of 2 ml (100 mg) of iron dextran until the calculated total amount has been administered. Another popular method uses total-dose intravenous infusion of iron dextran. It is recommended that iron dextran be diluted in 200 to 250 ml normal saline, infused initially at a rate that delivers a test dose of 25 mg over five minutes. If no reactions occur, the remaining volume may be infused over the next one to two hours. If iron dextran is diluted in 5 percent dextrose and water, local phlebitis frequently occurs.

Immediate and delayed systemic reactions may occur with either the intravenous or intramuscular route.[21] Immediate reactions usually occur within five minutes and may appear as life-threatening anaphylactoid reactions characterized by hypotension, syncope, purpura, wheezing, dyspnea, respiratory arrest and cyanosis. Less severe reactions are characterized by transient hypotension, malaise, itching and urticaria lasting approximately five minutes. On the other hand, delayed systemic reactions, lymphadenopathy, myalgia, fever and headache typically begin 4 to 48 hours after injection and persist from three to seven days. Because of the risk of lethal reactions with parenteral iron therapy, physicians should avoid its routine use and administer oral therapy whenever feasible.

Anemia of Chronic Disease

Elderly patients with chronic inflammatory states such as rheumatoid arthritis, infections such as tuberculosis or osteomyelitis, neoplastic disease or, occasionally, liver or renal disease, frequently have anemia. The anemia is usually mild to moderate with hematocrit values ranging from 27 percent to 35 percent. The anemia is due to a defect in bone marrow production with a reduced compensatory marrow response to some shortening of the erythrocyte life span. A block in the release of iron from reticuloendothelial cells results in low plasma iron. This low concentration simulates iron deficiency and the patient sometimes mistakenly receives long-term iron therapy. There are many similarities in laboratory findings of anemia of chronic disease and iron deficiency anemia.[8,22] Either may display a normochromic or hypochromic anemia, low reticulocyte indices, low serum iron concentration and elevated erythrocyte protoporphyrin levels. An elevated TIBC confirms a diagnosis of iron deficiency; however, because many patients with iron deficiency have a normal or low TIBC in association with low serum iron levels, this test often does not distinguish between them. However, the serum ferritin value is low in iron deficiency anemia, whereas in the anemia of chronic disease the value is high normal or elevated.

Sideroblastic Anemia

An elderly patient with hypochromia, who is not iron deficient and who does not have evidence of chronic disease, is likely to have sideroblastic anemia. Erythropoiesis is impaired due to defective heme synthesis, producing a hypochromic anemia associated with tissue iron overload. The serum iron is increased and the iron saturation of transferrin is often close to 100 percent. Iron does not combine with protoporphyrin to form heme. Instead, iron accumulation within the mitochondria of marrow nucleated erythroid cells forms ring sideroblasts; these are diagnostic for sideroblastic anemia.

Vitamin B_{12} and Folate Deficiency

Nutritional folate deficiency is found more frequently than vitamin B_{12} deficiency in the elderly. Poor dietary intake is more prevalent in persons living alone and in alcoholics. Older people who live alone with no social interaction have little incentive for preparing meals, and some live virtually on tea and toast. Folate deficiency is liable to develop in elderly people whose diet does not include uncooked fruit, fruit juice or fresh vegetables.

On the other hand, vitamin B_{12} is found in foods of animal origin, including meat, poultry, fish, eggs and dairy products. It is not found in plant sources; therefore, vitamin B_{12} deficiency may develop in old people adhering to a vegetarian diet. Vitamin B_{12} deficiency also occurs in elderly persons with pernicious anemia and in those who have had a total gastrectomy because of absent gastric intrinsic factor. However, more subtle forms of vitamin B_{12} deficiency occur even in the presence of adequate intrinsic factor as a result of insufficient gastric secretions to liberate vitamin B_{12} from food in patients with partial gastrectomy, vagotomy with gastroenterostomy or chronic gastritis with achlorhydria or hypochlorhydria.[23] In this situation, orally administered radioactive vitamin B_{12} would be normally absorbed, thereby resulting in a normal Schilling

test result. Obviously, removal of ileal receptors for vitamin B_{12} in the terminal ileum by either surgical resection or disease (such as regional ileitis) results in malabsorption of vitamin B_{12}.

Abnormalities of the blood and bone marrow are similar for vitamin B_{12} or folate deficiency, and are characterized by macro-ovalocytes and hypersegmented neutrophils in the peripheral blood, mean corpuscular volume greater than 100 μ^3, thrombocytopenia, leukopenia, bone marrow megaloblastosis, increased serum lactate dehydrogenase and elevated serum bilirubin levels. Measurement of serum levels of vitamin B_{12} and folate distinguish these deficiencies. The clinical and initial laboratory results should direct the physician's course in marshaling a proper sequence of tests for diagnosis. Occasionally, a clinician may wander from the accepted ritual and may, for example, decide against a bone marrow study in a patient with a high mean corpuscular volume, macro-ovalocytes, hypersegmented polymorphonuclear leukocytes and a low serum B_{12} level, who predictably will have a megaloblastic bone marrow.

Serum vitamin B_{12} tests are widely available as cobalamin (vitamin B_{12}) radioassay kits for the diagnosis of vitamin B_{12} deficiency. Several of the commercially available kits contain nonspecific R-protein, which binds both metabolically active and inactive forms of the vitamin, thereby giving falsely normal results in patients who are actually vitamin B_{12} deficient.[24-27] Kits that contain only intrinsic factor as the binding agent are more reliable. Clinically, if the possibility of vitamin B_{12} deficiency exists, despite a normal serum vitamin B_{12} radioassay level, a Schilling test should be done to help clarify the issue.

Treatment with folic acid will produce a hematologic remission even in patients with vitamin B_{12} deficiency. This may be dangerous because in such a patient, the vitamin B_{12} deficiency may progress to an irreversible neuropathy. Therefore, a correct diagnosis is essential before treatment. Vitamin B_{12} deficiency is treated with hydroxocobalamin. Initial therapy consists of 1,000 μg injected intramuscularly every two to three days for six injections. This is followed by maintenance therapy of 500 to 1,000 μg given intramuscularly every three months. If immediate therapy is indicated before establishing the specific deficiency responsible, a blood specimen is drawn for serum assays of both folate and vitamin B_{12}. Therapy should be initiated with both folate and vitamin B_{12} and the appropriate therapy continued as indicated by the results of the serum assay. Patients who have had a gastrectomy or ileal resection should receive a dose of 1,000 μg of hydroxocobalamin every three months as preventive therapy.

A dose of 1 mg per day of folic acid taken orally is sufficient for therapy of folate deficiency. The length of therapy depends on the underlying cause but is usually four months.

Acute Leukemia

Acute nonlymphocytic leukemia (myeloblastic) is primarily a disease of the elderly. Seventy percent of patients are 50 years of age or older. Until recently it has been inferred that acute leukemia in those older than 60 is refractory to therapy, and that bone marrow aplasia resulting from therapy is poorly tolerated. Recently, however, elderly patients have been achieving complete remissions followed by long survival.[28-30]

Acute leukemia in younger patients has an abrupt onset, whereas approximately 30 percent of elderly patients have a preleukemic phase. Elderly patients have nonspecific complaints such as malaise, anorexia, weight loss and weakness. Other symptoms include fatigue (due to anemia), bleeding and bruising (due to thrombocytopenia or disseminated intravascular coagulopathy), fever (due to infections), bone and joint pain, lymphadenopathy, hepatosplenomegaly and neurological symptoms resulting from leukemic infiltrates.

Infection is a common complication and cause of death. Neutropenia caused by leukemia or its treatment is the most important factor in producing susceptibility to infection. In any patient with fewer than 1,000 neutrophils per cu mm, the presence of an unexplained temperature higher than 38.5°C (101°F) should be considered an emergency, requiring immediate antibiotic therapy.

Laboratory studies show anemia, thrombocytopenia and granulocytopenia with myeloblasts or monoblasts, or both, in the peripheral blood. The marrow is usually hypercellular with myeloblasts, monocytoid features of the granulocytic cells and, sometimes, megaloblastic changes of the erythroid cells and atypical megakaryocytes.

If untreated, the mean duration from onset of symptoms to death is less than six months. With combination chemotherapy, a remission rate of 20 percent to 50 percent has been achieved in patients older than 50. This is lower than the

remission rate of 50 percent to 80 percent for all ages. This difference may be a result of prolonged marrow hypoplasia during chemotherapy, the presence of other diseases, diminished physiological reserve capacity and decreased immune competence. The median survival time is approximately 10 to 22 months[28-30]; however, a few older patients achieving complete remission have remained in remission five years or longer. These encouraging results have caused physicians to consider seriously treatment of acute leukemia in the elderly. The crucial dilemma is to decide who shall be treated. Judgment should not be made on the basis of age alone. Acute leukemia is uniformly fatal and, therefore, aggressive therapy is indicated regardless of age. Newer regimens have been highly effective in patients up to 70 years of age, and complete remissions have been induced in patients in the ninth decade of life.[31] On the other hand, the risk of therapy and its complications should not be imposed on patients who have an impoverished quality of life as a result of impairment of physical and mental function. With older patients, it is as important to learn when not to treat as when to treat and each situation must be carefully assessed to arrive at a reasonable decision.

Some elderly patients have "smoldering" leukemia, which is characterized by mildly elevated leukocyte counts, with relatively few myeloblasts, anemia and a tendency to infection or hemorrhage. The leukemia has a slow course over several years and requires no chemotherapy. These patients, however, eventually progress to a more acute stage where specific antileukemic therapy is indicated.

Preleukemia often precedes the development of acute nonlymphocytic leukemia.[32,33] It occurs in approximately 30 percent of elderly patients in whom acute nonlymphocytic leukemia develops. The bone marrow exhibits erythroid hyperplasia with prominent megaloblastic features and multinucleated forms. Ring sideroblasts are frequently observed and atypical megakaryocytes are seen. Monocytosis and monocytoid granulocytic cells may be observed. Peripheral blood shows variable-sized erythrocytes with macro-ovalocytes and, occasionally, circulating nucleated red cells. The hematological picture may be confused with vitamin B_{12} or folate deficiency; however, serum vitamin B_{12} and folate levels should be normal and treatment with these medications is ineffective. A preleukemic syndrome often persists for 6 to 24 months before the development of overt leukemia. Occasionally, cases have lasted as long as five to ten years. There is no specific treatment for the preleukemic syndrome except for supportive therapy with transfusions or intermittent platelet transfusions for anemia and severe thrombocytopenia, respectively. A few patients have responded to treatment with prednisone, and in vitro marrow cultures may assist in determining those patients who are likely to achieve success with corticosteroid therapy.[34]

Chronic Lymphocytic Leukemia

This is the most frequent leukemia in the elderly and 80 percent of new diagnoses are made in patients over 50 years of age. Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by excessive lymphocytes in the bone marrow accompanied by lymphocytosis in the peripheral blood. Eventually, in the course of the disease, lymphocytes replace normal marrow, thereby inducing anemia, thrombocytopenia, and neutropenia. The course of the disease is variable and it is not unusual to follow some patients for 10 to 15 years. Unfortunately, a more aggressive course ensues with some patients and CLL can no longer be viewed as an indolent disease afflicting the elderly. Susceptibility to infection is related to hypogammaglobulinemia, poor cellular immune response and granulocytopenia. Anemia and thrombocytopenia result from bone marrow replacement with leukemic cells, chemotherapy or hypersplenism. In approximately 20 percent of patients, a Coombs'-positive autoimmune anemia will develop and, less frequently, an autoimmune thrombocytopenia that may respond dramatically to corticosteroid therapy.

With the benign form of CLL, the patient requires no therapy for the leukemia. However, with aggressive disease, alkylating agents such as chlorambucil and cyclophosphamide are effective in returning blood counts to normal and reducing lymphadenopathy, splenomegaly and hepatomegaly. Chlorambucil is the agent most commonly used. Prednisone, along with an alkylating agent, is beneficial for cytopenias resulting from lymphocytic bone marrow infiltration, autoimmune hemolysis or thrombocytopenia or hypersplenism. The administration of allopurinol and maintenance of good hydration during therapy prevents formation of uric acid stones and nephropathy from excessive uric acid liberated as a result of cell destruction. Radiation therapy is

especially useful for bulky adenopathy or localized lymphocytic infiltration that causes blockage of ureters, bile ducts or bronchi. Splenectomy has been helpful in a few patients with prednisone-resistant hypersplenism and severe cytopenia. Leukapheresis removes significant numbers of lymphocytes and is especially suitable for management of patients with significant anemia and thrombocytopenia.

Multiple Myeloma

With growing numbers of elderly people and better methods of diagnosis, the incidence of myeloma is increasingly recognized especially in those after age 60. Myeloma results from a selective proliferation of a single clone of lymphocytes (B cells), which produces a specific immunoglobulin. The latter serves as a tumor marker, indicating the size of the myeloma cell mass.[35] This myeloma protein produces a spike on serum protein electrophoresis. The frequency of types of protein abnormalities found in patients with myeloma are: IgG 61 percent, light chain 19.5 percent, IgA 17 percent, IgD 1.5 percent and IgE less than 1 percent.[36]

Major features of myeloma are plasma cell infiltration of the bone marrow, monoclonal gammopathy of serum or urine, osteolytic lesions or osteoporosis, hypercalcemia, anemia and azotemia. The most prominent symptom is bone pain due to myeloma cells in the marrow cavity causing osteolytic lesions or osteoporosis. Osteoporosis may be the only bone lesion in 25 percent of cases. An osteoclastic-activating factor produced by abnormal plasma cells causes this bone resorption and leads to hypercalcemia.[37] Myeloma should be suspected in an elderly patient with bone pain who has an unexplained anemia, particularly with rouleux formation on the peripheral blood smear. Routine analysis of urine and "dip stick" methods will not detect Bence-Jones protein, whereas sulfosalicylic acid and p-toluene sulfonic acid are good screening methods. Positive results should always be confirmed by electrophoresis and immunoelectrophoresis of concentrated urine. A monoclonal spike is not always diagnostic of multiple myeloma because approximately 1 percent to 3 percent of elderly persons have monoclonal gammopathy but myeloma does not develop. These have been called "benign" idiopathic monoclonal gammopathy and are distinguished from myeloma by a monoclonal spike seldom greater than 1 gram per dl, less than 20 percent marrow plasma cells, absence of Bence-Jones proteinuria and no apparent bone destruction.

Renal failure is a significant negative prognostic sign in myeloma. Tubular destruction secondary to a light chain proteinuria (Bence-Jones proteins) produces the typical myeloma kidney. Hypercalcemia is a treatable cause of renal failure. Hyperuricemia often occurs after initiating treatment. It should be anticipated and thereby prevented by adequate hydration and allopurinol therapy. Complications produced by urate precipitation in renal tubules or ureters, which induce ureteral colic, azotemia or oliguria, are therefore prevented. Other causes of chronic renal failure in myeloma are amyloidosis, plasma cell infiltration of the kidneys and pyelonephritis. Acute renal failure is a common complication of intravenous pyelography in myeloma patients. This procedure should be done only if absolutely necessary, and the patient should always be well hydrated.

Infection is the major complication and cause of death in patients with myeloma. Pneumonia and urinary tract infections are common and should be promptly diagnosed and treated. Many complications of myeloma such as infection, hypercalcemia, hyperuricemia, anemia, hyperviscosity and pathological fractures can be anticipated and prevented, or minimized, by appropriate therapy. Patients with multiple myeloma have a mean survival of seven months from the time of diagnosis. Treatment with chemotherapy and supportive measures increases median survival time to 23 to 40 months. Radiation therapy is effective for relief of localized pain caused by myelomatous lesions. Tumor compression of the spinal cord is an emergency and should be treated promptly.[38] Either radiation therapy or laminectomy followed by radiation therapy, is indicated for neurological symptoms, depending on their severity.

Waldenstrom's Macroglobulinemia

Waldenstrom's macroglobulinemia is a disease of the elderly distinguished by a high concentration of monoclonal IgM macroglobulins, which produce a hyperviscosity syndrome. Dilatation of retinal veins, loss of vision, impaired hearing, skin or mucosal bleeding, congestive heart failure, headache, dizziness and coma may ensue. The bone marrow is infiltrated with cells that have the characteristics of both plasma cells and lymphocytes. Plasmapheresis effectively reverses the symptoms of the hyperviscosity syndrome. Chem-

otherapy reduces the cellular infiltrate and further inhibits production of immunoglobulin.

Agnogenic Myeloid Metaplasia

The distinguishing feature is extramedullary hemopoiesis with cellular proliferation in the spleen, liver and lymph nodes. The peripheral blood shows teardrop-shaped erythrocytes, nucleated erythrocytes, immature granulocytes and abnormal platelets. The leukocyte count is frequently elevated, usually less than 30,000 per cu mm. Platelet counts may be low, normal or high. Bone marrow biopsy specimens show fibrosis, and the spleen is enlarged, usually hard and irregular.

Elderly patients with agnogenic myeloid metaplasia may have severe symptoms, requiring blood transfusions to treat anemia. Androgens have not been beneficial. Thrombocytosis has been associated with either bleeding or thrombosis and is especially troublesome when platelet counts are more than 1,000,000 per cu mm. Aspirin and other antiplatelet agents are helpful for the hypercoagulable state resulting from thrombocytosis.[39] Chemotherapy with agents such as busulfan, chlorambucil or cyclophosphamide decreases platelets and often reduces splenic size. Splenectomy[40] is reserved for some cases of severe thrombocytopenia or hemolytic anemia, which are unresponsive to medical therapy, splenic infarcts, symptoms due to massive splenomegaly, and portal hypertension with bleeding.

Polycythemia Vera

Polycythemia vera is characterized by hyperplasia of the bone marrow with increased numbers of circulating erythrocytes, granulocytes and platelets. Measurement of erythrocyte volume, using erythrocytes labeled with ^{51}Cr, is necessary to establish absolute erythrocytosis. The two major categories of absolute erythrocytosis are polycythemia vera and erythropoietin-producing disorders, or secondary erythrocytosis. The latter are several times more common than polycythemia vera and involve only erythropoiesis. A history of cigarette smoking should be sought before carrying out an extensive diagnostic evaluation for an increased hematocrit level. Cigarette smoking increases erythrocyte volume by binding carbon monoxide to hemoglobin to produce carboxyhemoglobin, which does not bind oxygen. Smoking also reduces plasma volume, which accentuates the increased hematocrit.

Determination of arterial oxygen saturation is an initial step in the evaluation, and a level of less than 92 percent warrants a diagnosis of secondary erythrocytosis and implies a need to investigate cardiac and pulmonary causes. If the arterial oxygen saturation is more than 92 percent, other causes of inappropriately increased erythropoietin activity may be associated with renal tumors, cysts, hydronephrosis, renal parenchymal disease and paraneoplastic syndromes associated with tumors of the liver (hepatoma), ovary, adrenal gland and cerebellum. Polycythemia vera is easier to diagnose if erythrocytosis is accompanied by leukocytosis, thrombocytosis or splenomegaly. Rarely, in the presence of abnormal hemoglobins, an increase in affinity for oxygen leads to tissue hypoxia and increased erythropoietin production with consequent erythrocytosis. Recent reviews provide better insight into diagnostic approaches.[41,42]

After definitive diagnosis, phlebotomy treatment should be considered for both polycythemia vera and secondary erythrocytosis, but only after precipitating factors have been corrected. Discontinuation of smoking, oxygen therapy for chronic lung disease, weight reduction for the obesity-hypoventilation syndrome and surgical removal of erythropoietin-producing tumors may correct erythrocytosis. Reduced cerebral blood flow with the risk of thromboembolism exists with hematocrits of 60 percent. Early reduction of hematocrit to 45 percent increases cerebral blood flow and reduces blood viscosity.[43] In elderly patients with chronic obstructive lung disease and secondary erythrocytosis, there is resolution of dizziness and headaches after venesection, concomitant with a significant decrease in the hematocrit and blood viscosity and an increase of cerebral blood flow.[44]

For polycythemia vera, radioactive phosphorus (^{32}P) is the treatment of choice. Recently, the Polycythemia Vera Study Group has reported a higher incidence of acute leukemia in chlorambucil-treated patients than in patients treated with phlebotomy or ^{32}P therapy.[45] Therefore, ^{32}P is the treatment of choice for patients whose condition cannot be controlled by phlebotomy alone.

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Drug Prescribing for the Elderly

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Age-related biologic and physiologic changes, the accumulation of multiple pathologic conditions with increasing age and several socioeconomic considerations combine to make drug prescribing for the elderly one of the most challenging tasks in clinical medicine. Numerous studies in older persons have documented alterations in the pharmacology of many drugs. Several general recommendations are presented which should make drug prescribing for elderly patients safer and more effective.

PRESCRIPTION MEDICATIONS represent a substantial portion of this country's ever-growing health care expenditures. They are not covered by many insurance plans for the elderly, and this can cause considerable out-of-pocket expense from what is often a fixed and limited income.

It is not unusual that several different drugs are prescribed for an elderly patient, to be taken on complex dosage schedules. This is especially so in acute care hospitals, where Medicare patients receive an average of ten prescription drugs,[1] and in nursing homes, where many of the four to seven drugs prescribed for each patient are inappropriate or ineffective.[2]

Drugs are a major cause of iatrogenic illnesses, conditions which are disturbingly common.[3,4] One recent study found an iatrogenic illness in more than a third of patients on the medical service of a university hospital,[4] and drugs were one of the most important factors in the development of these complications. Older persons are particularly susceptible to adverse drug reactions; the incidence of adverse reactions in hospitals increases from 3 percent in those aged 10 to 30[5] to close to 25 percent in those older than age 80.[6] These reactions contribute to more than 10 percent of admissions to geriatric departments in Great Britain,[7] and account for as many as 3 percent of all admissions to US hospitals.[8] As much as $3 billion per year may be spent in this country as a result of adverse drug reactions.[2]

Given these costs, in both health and dollars, physicians should become aware of some of the complex considerations that attend prescribing for the elderly. Age-related biologic and physiologic changes, the accumulation of multiple pathologic conditions with increasing age and several socioeconomic factors combine to make prescribing drugs one of the most difficult, yet challenging, aspects of caring for these patients.

This article will briefly review age-related changes that are relevant to drug prescribing, and make several recommendations which are designed to make treatment of the elderly with drugs safer and more effective.

Age-Related Changes Relevant to Drug Prescribing

Altered Reporting and Presentation of Illness

Altered reporting and presentation of illness can make accurate diagnosis, and therefore appropriate drug prescription, more difficult in

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elderly patients. Impairments of hearing and vision, dementia and depression can all compromise a patient's ability to communicate symptoms. Vague and multiple somatic symptoms, extremely common in the elderly, often represent psychic distress rather than physical illness.[9] Interpretation of these symptoms for physical illness, or exacerbation of an underlying medical condition, can result in inappropriate drug treatment.

Even when physical illnesses are present, they may be difficult to diagnose. Confusion, falls and urinary incontinence may be the presenting manifestations of a variety of treatable disorders; conditions such as hyperthyroidism and myocardial infarction may present with vague or nonspecific symptoms. As a result, treatable conditions can go unrecognized in this population.[10,11] Left unrecognized, these disorders will not only remain untreated but may be exacerbated by drug treatment, or may alter the success of drug treatment for another illness.

Age-Related Biologic and Physiologic Changes

Age-related changes occur in many biologic and physiologic functions.[12] Table 1 lists several types of changes that can affect the pharmacology of many drugs.

It is crucial to keep in mind two characteristics of changes that occur with age. First, the changes are gradual and occur over many years. Second, there is wide interindividual variation in the rate of these age-related changes. Thus, although advancing age is associated with the decline in many physiologic functions, the extent of decline in any individual person is difficult to predict. This is important to remember when prescribing drugs; applying average age-related changes in physiologic functions to a particular older patient can be misleading, and may result in overdosage, as well as underdosage, of many drugs.

Absorption. As shown in Table 1, there are several age-related changes that could affect the absorption of drugs in the elderly.[13] Although several studies of drug absorption in this population have been carried out,[14] none have shown clinically meaningful changes. Altered absorption of drugs, therefore, appears to be the least important of age-related changes in pharmacology.

Distribution. Several changes related to age can affect the distribution of drugs. Alterations in blood flow, especially to the major sites of drug elimination (liver, kidney) can have important influences on drug kinetics and effects.[15] Changes in body composition, such as increased fat and decreased extracellular fluid and lean body mass,[16] can alter the concentration and kinetics of drugs that distribute in the various body compartments. Decline in serum albumin,[17] the major drug binding protein, can make more free drug available for pharmacologic action. The combination of lower serum albumin and polypharmacy may result in many adverse drug interactions—especially involving those drugs that are highly protein bound, such as salicylates, anticoagulants and orally given hypoglycemics.

TABLE 1.—*Age-Related Changes Relevant to Pharmacology*

Age-Related Change	*Pharmacologic Function*
Decreased absorptive surface Decreased splanchnic blood flow Increased gastric pH Altered gastrointestinal motility	Absorption
Decreased lean body mass Decreased total body water Decreased serum albumin Increased fat Altered protein binding	Distribution
Decreased liver mass Decreased liver blood flow Decreased enzyme activity and inducibility	Hepatic metabolism
Decreased renal blood flow Decreased glomerular filtration rate Decreased tubular secretory function	Renal excretion
Alterations in Receptor number Receptor affinity Second messenger function Cellular responses	Receptor sensitivity

Hepatic Metabolism. Although there are no age-related changes in routine liver function tests, the liver's capacity to metabolize drugs is altered with increasing age. Because blood flow to the liver declines,[15] first-pass hepatic extraction and metabolism of orally administered drugs is diminished. The ability of environmental factors, such as cigarette smoking, to induce drug metabolizing enzymes decreases with age.[18-20] Studies of age-related changes in specific hepatic drug metabolic pathways, such as oxidation, hydroxylation and acetylation, have shown variable results.[14,21,22] The effects of aging on hepatic drug metabolism are therefore complex, dependent on several factors and often difficult to predict.

Excretion. Several structural and functional changes occur in the kidney with increasing age[23] that have important influences on the excretion of drugs and their active metabolites (Table 1).

Because lean body mass declines with age, daily

TABLE 2.—*Important Considerations in Prescribing for the Elderly**

Drugs	*Pharmacokinetic Considerations*	*Other Considerations*
ANALGESICS		
Nonnarcotic	Aspirin may have longer duration of action and half-life may be prolonged at higher doses.	Aspirin, nonsteroidal antiinflammatory agents and acetaminophen generally of equivalent efficacy; latter may be less toxic.
		Salicylate blood levels may be helpful.
Narcotic	Morphine blood levels higher and duration of pain relief longer.	Lower doses of most narcotics may give adequate analgesia and less central nervous system and respiratory depression.
ANTIMICROBIALS	Penicillins (except nafcillin), aminoglycosides, cephalosporins, tetracyclines (except doxycycline) eliminated predominantly by kidney and may have prolonged half-lives and higher steady-state blood levels.	Aminoglycoside blood levels helpful.
		Isoniazid toxicity increases with age.
		Intravenous carbenicillin gives substantial sodium load.
CANCER CHEMOTHERAPY		No change in toxicity or efficacy with protocols for lung, breast, colon.
CARDIOVASCULAR AGENTS		
Antiarrhythmics	Lidocaine has increased volume of distribution and prolonged half-life.	Lidocaine, quinidine and procainamide blood levels helpful.
	Quinidine and procainamide have prolonged half-lives and higher steady-state blood levels.	Disopyramide may have prominent anticholinergic effects, especially blurry vision and urinary retention.
		Lidocaine may cause confusion at high doses.
Anticoagulants		Lower doses of warfarin needed for anticoagulation.
		Bleeding complications may be more frequent.
Antihypertensives		Sodium restriction and weight reduction may be effective when practical.
Diuretics		Elderly predisposed to dehydration and electrolyte imbalance.
		Thiazides and furosemide may exacerbate glucose tolerance.
		Potassium sparing agents (or supplementation) necessary in some (especially with digoxin), but may cause hyperkalemia in others.
Other agents	Propranolol has prolonged half-life and higher blood levels.	Propranolol often effective despite possible diminished sensitivity to cardiac effects. Incidence of adverse reactions higher, especially in patients with heart failure, bronchospasm, bradycardia or heart block, and those receiving hypoglycemic agents.
	Metoprolol may have higher blood levels.	
	Clonidine and methyldopa eliminated predominantly by kidney and may have prolonged half-life.	Hydralazine may not cause reflex tachycardia but may exacerbate angina in some.
		Postural hypotension occurs in many even before therapy.
		Clonidine and prazosin usually do not cause postural hypotension with chronic therapy.
Digoxin	May have prolonged half-life and higher steady-state blood levels.	Blood levels helpful.
		May not be efficacious in chronic stable heart failure with sinus rhythm.
PSYCHOACTIVE AGENTS		
Antidepressants	Amitriptyline, imipramine and lithium may have higher blood levels.	Desipramine has the least anticholinergic and sedative effects.
		All tricyclics can cause postural hypotension; should be used carefully when antihypertensives have been prescribed.
		Doxepin may have less cardiotoxicity.
		Tricyclic blood levels may be helpful.

*After Ouslander JG: Drug Therapy in the Elderly. Annals of Internal Medicine, in press.

(Continued on next page)

TABLE 2.—*Important Considerations in Prescribing for the Elderly (Continued)*

Drugs	*Pharmacokinetic Considerations*	*Other Considerations*
		Lithium blood levels important to avoid toxicity.
Antipsychotic		Lower doses of phenothizines and haloperidol generally effective and safer.
Sedative/hypnotic ...	Diazepam has prolonged half-life, especially in men.	Complaints of sleep disturbance may represent age-related changes in sleep patterns.
	Oxazepam and lorazepam kinetics unchanged, and have shorter half-lives than other benzodiazepines.	Nonpharmacologic measures often effective for sleep disturbances.
		Increased sensitivity to effects of diazepam.
		Flurazepam more toxic in doses over 15 mg.
		Chloral hydrate generally safe and effective in doses up to 1 gram.
		Diphenhydramine may increase confusion in some.
OTHER DRUGS		
Aminophylline	Less needed by intravenous infusion for therapeutic blood levels; half-life may be prolonged.	Blood levels helpful.
Cimetidine	Half-life may be prolonged and steady-state blood levels higher.	May cause confusion at higher doses.
Hypoglycemic agents .	Eliminated predominantly by kidney (except chlorpropamide); tolbutamide has shortest half-life and may be cleared more rapidly; acetohexamide and tolazamide have intermediate duration of action (close to 24 hours).	Chlorpropramide may cause hyponatremia and prolonged hypoglycemia and is not generally indicated.
		Intermediate-acting drugs probably first choice given once per day.
Levodopa		Routine doses may cause confusion and postural hypotension.
Phenytoin	Steady-state blood levels may be higher.	Blood levels helpful.
Thyroxine	Metabolic clearance may be prolonged.	Maintenance dose may be lower.
		Thyroid stimulating hormone level helpful in following response.

endogenous creatinine production declines. Serum creatinine may therefore be "normal" in an elderly person, and may not reflect a substantial decline in creatinine clearance. Glomerular filtration rate declines an average of 35 percent between the ages of 20 and 90.[24] Formulae and nomograms have been developed to estimate true creatinine clearance in relation to age.[25,26] One such formula is shown below:

$$\text{creatinine clearance} = \frac{(140 - \text{age}) \times \text{body wt (kg)}}{72 \times \text{serum creatinine}}$$

This result should be multiplied by 0.85 for women.[26]

This formula can be useful to determine initial doses of drugs that are eliminated predominantly by renal excretion (such as aminoglycosides, cephalosporins, digoxin and procainamide).

Because of the interindividual variation in these age-related changes, and factors such as dehydration and heart failure which are often present in ill elderly patients, determinations of creatinine clearance and blood drug levels may be more useful when available.

Receptor Sensitivity. It is often stated that old persons are more sensitive to drug effects. Recent studies of several drugs have shown age-related pharmacodynamic changes (altered drug effects that cannot be explained by pharmacokinetic changes). The elderly appear to be more sensitive than younger persons to the effects of given blood levels of diazepam[27] and warfarin,[28] yet less sensitive to the cardiac effects of isoproterenol and propranolol.[29] Although there are several potential mechanisms for these observations (Table 1), further research is necessary to more precisely define the underlying bases for these changes.

Pharmacology of Specific Drugs in the Elderly

Numerous studies have documented changes in the pharmacokinetics of many drugs in the elderly. It is beyond the scope of this review to describe these studies in detail; the reader is referred to

several recent reviews and texts that discuss these studies in depth.[14,30-34]

Despite the large number of studies that have been done, it is difficult to make specific recommendations as to how to alter drug dosages for individual elderly patients. Several factors make the development of guidelines, such as those available for altering drug dosages in renal failure,[35] very complex. These factors include the wide interindividual variation of age-related changes, the coexistence of multiple conditions, the variability of the clinical status of individual elderly patients and the technical difficulties involved in defining age-related pharmacokinetic changes.[36]

Table 2 and the discussion below briefly summarize pharmacologic information that is particularly relevant to the prescription of specific drugs for the elderly.

Analgesics

Many elderly persons frequently complain of pain. It is important to attempt to differentiate pain from an inflammatory process from noninflammatory causes, because the former may respond more favorably to aspirin and nonsteroidal inflammatory drugs. These drugs are of generally equivalent efficacy; the half-life of aspirin is increased in older persons, and may be greatly increased at higher doses. Determinations of salicylate blood levels may be helpful when high doses are used. Acetominophen is safe in the elderly; it should be kept in mind that many patients with minor pain may benefit by nonpharmacologic treatments.

Narcotic analgesics appear to give more pain relief, and may have prolonged duration of action, in older patients.[37] These drugs can cause sedation, confusion and severe constipation (which can lead to fecal impaction and its attendant problems) in the elderly; the need for these drugs should be carefully assessed, therefore, and their use closely monitored.

Antimicrobials

Most antimicrobial drugs are eliminated predominantly by renal excretion (Table 2). Age-related changes in renal function should not influence the standard dosages of most of these drugs; aminoglycosides, because of their potential for ototoxicity and nephrotoxicity, should be used carefully. Blood level determinations may be useful when using these agents.

Two antimicrobial agents may have special potential for adverse reactions in old persons. Intravenously administered carbenicillin delivers a substantial sodium load, and should be used carefully in patients with symptomatic congestive heart failure. Isoniazid hepatotoxicity increases with age and its use should be carefully evaluated and monitored.[38]

Cancer Chemotherapy

A recent analysis of data from the Eastern Cooperative Oncology Group showed that toxicity from protocols for lung, breast and colon cancer does not increase in the elderly.[39] This was true despite the lack of any dosage reductions; the regimens also were equally effective in the older age groups.

Cardiovascular Agents

Antiarrhythmics. Arrhythmias are common in the elderly, but because of the potential toxicity of antiarrhythmic agents, the necessity for treatment should be carefully evaluated. Lidocaine, quinidine and procainamide all have prolonged half-lives in the elderly; the latter two drugs also have higher steady-state blood levels.[40,41] Blood levels of these agents can be helpful in monitoring therapy. Disopyramide can cause prominent anticholinergic side effects in these patients, such as urinary retention and blurry vision. Other newer antiarrhythmics have not been well studied in older persons.

Antihypertensives. The management of hypertension in the elderly remains controversial.[42,43] Although data are scarce in the very old (older than 75), recent studies involving persons between 60 and 69 years of age indicate that hypertension remains an important risk factor for cardiovascular morbidity and mortality,[44,45] and that treatment may reduce this risk.[46]

Antihypertensives may, however, produce serious adverse reactions in the elderly. Diuretics may predispose to electrolyte imbalance and dehydration, especially when an intercurrent illness decreases oral intake. They may also exacerbate urinary incontinence. Postural hypotension is common even without drugs, and may be exacerbated by most antihypertensive agents. This may lead to falls and their sequelae; lethargy, depression and confusion may also result from antihypertensive agents.

β-Adrenergic blocking agents, although useful for hypertension as well as angina, must be used

carefully in the elderly. The incidence of adverse reactions is higher,[47] especially with chronic obstructive lung disease, congestive heart failure, bradycardia and concurrent hypoglycemic therapy. Although there is some evidence that old persons are less sensitive to the cardiac effects of propranolol,[29] its metabolism is diminished, half-life prolonged and blood levels higher.[19,48]

The potential benefits of antihypertensive therapy must be carefully weighed against the possible adverse effects on the quality of life. Restrictive diets, although helpful in some, may be unpalatable and impractical for many elderly persons. The reader is referred to recent reviews for more detailed suggestions on the management of hypertension in this population.[42,43]

Digoxin. Digoxin is one of the most frequently prescribed yet potentially toxic drugs in the elderly.[7,31] Recent studies have suggested that persons with chronic heart failure in sinus rhythm can be safely withdrawn from therapy,[49,50] although this remains controversial.[51] Because of its potential toxicity, the necessity for this agent should be carefully evaluated (it should not be given for nonspecific symptoms alone, such as fatigue, dyspnea or lower extremity edema). Blood levels may be helpful in determining compliance and toxicity. Toxicity may be especially difficult to diagnose because the manifestations are often nonspecific (such as fatigue and weakness).[52]

Psychoactive Drugs

Despite considerable evidence that psychoactive drugs have enhanced toxicity in older persons,[53-55] they are commonly used in this population; 75 percent of nursing home residents receive at least one of these drugs and usually more.[56]

Although the judicious use of these drugs can provide dramatic relief of the anxiety, agitation and depression so common in the elderly, it should be remembered that these symptoms may reflect underlying physical illness.[8] Excessive sedation may result from many of these drugs, especially hypnotics such as flurazepam (when given in doses of 30 mg or more).[55] Many of these agents have prominent anticholinergic effects (especially amitriptyline, doxepin, thorazine and thioridazine) and can cause confusion, blurry vision, urinary retention and constipation. Tricyclic antidepressants can cause postural hypotension (especially when added to an antihypertensive agent) and falls, as well as prolonged cardiac conduction. They must be used very carefully in older patients with underlying cardiovascular disease.[57] Many of these drugs (especially antipsychotic drugs such as haloperidol and thioridazine) can have prominent extrapyramidal side effects, and can exacerbate underlying Parkinson's disease and other gait disturbances in these patients.

Although numerous drugs have been used to improve cognitive function in the elderly, none have been shown in rigorously controlled studies to have substantial impact on daily functional capabilities. Until further research yields better drugs, these agents (which are often very expensive) should not replace careful evaluation and follow-up of cognitive impairment, and counseling of the patient and family.

The reader is referred to recent comprehensive reviews that deal in depth with psychoactive drug use in the elderly.[32,58]

Other Drugs

Important considerations for other commonly used drugs in the elderly, such as aminophylline, cimetadine and oral hypoglycemic agents are shown in Table 2.

Compliance

Compliance is often a major obstacle to drug treatment in any population. Most studies show between a third and a half of patients will fail to comply with a medical regimen.[59]

Several factors make compliance an even more complex feature of drug prescribing in the elderly. Mild and chronic disorders that require prophylactic or suppressive therapy, and in which the consequences of stopping therapy may be delayed, lend themselves to noncompliance. Complex medical regimens, requiring several different medications and frequent doses, may also contribute to a higher incidence of noncompliance. All of these are common in the elderly population.

In addition to the prevalence of mutiple chronic illnesses and the attendant need for complex drug regimens, a variety of physical, psychologic, social and economic barriers may impair an older patient's ability to comply.

The average elderly person in this country spends more than $100 a year on prescription drugs,[60] and these costs, usually not well covered by reimbursement plans, come out of an already fixed and limited income. Intellectual impairment, poor vision and diminished hearing may make patient education difficult, and prevent a patient

from following instructions. Many older persons have cultural attitudes and beliefs that may make the process even harder. Weakened, arthritic hands are often unable to open childproof containers, and this may be a problem in as many as 60 percent of elderly patients.[61] Lack of transportation or fear of crime may prevent the elderly from reaching a physician or pharmacist.

Many studies emphasize the need for careful supervision of elderly patients requiring long-term medication.[62,63] One of these showed that teaching a patient an individual drug regimen in the hospital may help identify and overcome problems with noncompliance.[64] Instructional aids such as tablet identification cards and tear-off calendars have also been shown to improve compliance in these patients.[64]

Recommendations

Although nomograms for specific dosage adjustments in the elderly have not been (and may never be) developed, there are several recommendations, shown in Table 3, that should be helpful in making drug prescribing safer and more effective. Special emphasis is placed in these recommendations on careful evaluation of the need for, and monitoring of, drug treatment; as well as the nonpharmacologic and socioeconomic aspects of drug prescribing for this population. In many instances, the latter considerations are more important to the efficacy of such drug prescribing than age-related changes in drug pharmacology.

TABLE 3.—*General Recommendation for Prescribing for the Elderly**

- Evaluate elderly patients for previously undiagnosed and treatable conditions that may affect, or be affected by drug therapy.
- Manage conditions without drugs as often as possible.
- Avoid interactions between newly prescribed drugs, drugs already being taken and underlying conditions.
- If there is any question about dosage, start with smaller doses and increase gradually.
- For drugs or their active metabolites eliminated predominantly by the kidney, formulae can be used to approximate age-related decline in renal function, and dosages adjusted accordingly.
- For drugs predominantly eliminated by hepatic metabolism, age-related changes are variable and difficult to predict in the absence of overt liver disease.
- Blood levels can be helpful in monitoring several potentially toxic drugs frequently used in the elderly.
- Individually tailor and simplify the drug regimen as much as possible.
- Pay special attention to impaired intellect, poor vision and diminished hearing when educating the patient and labeling the prescriptions.
- Help ensure compliance by asking if the patient has access to a pharmacy, can afford the prescription and can open the containers.
- Make use of relatives, friends, visiting health professionals and local pharmacists in helping the patient to comply.
- Monitor the patient frequently for compliance, drug effects and toxicity.

*After Ouslander JG: Drug Therapy in the Elderly. Annals of Internal Medicine, in press.

Summary

Many age-related biologic and physiologic changes can have important influences on drug pharmacology in elderly patients. Although numerous studies have been done, interindividual variation in the rates of age-related changes, differences in the clinical status of individual patients and technical difficulties in carrying out pharmacokinetic studies make it difficult to give specific recommendations for drug prescribing in older patients. Many socioeconomic and other nonpharmacologic factors have important influences on prescribing for this population.

Several general recommendations have been presented which should be helpful in prescribing for the elderly. As we gain more experience caring for this rapidly growing segment of our population, we are sure to achieve new insights into the complex and challenging task of safe and effective drug prescribing.

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Depression in Older Persons: Diagnosis and Management

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Depression is a common psychiatric disturbance of late life that is frequently not recognized by nonpsychiatric physicians. Confusion in psychiatric nosology, variability in clinical presentation, increased frequency of medical disease and medication use and cultural biases toward older persons complicate the diagnosis. Detection of depression is important because often this disorder can be successfully treated.

DEPRESSION is the most common psychiatric disorder of advanced age. Approximately 5 percent of the 25 million Americans older than 65 are depressed to a clinically recognizable degree.[1] Among elderly persons who have significant medical illness or who reside in institutions, depressive episodes may be even more common.[2] Depression in the elderly is associated with a high degree of morbidity.[3-5] Although members of this age group represent 11 percent of the population in the United States, they account for 25 percent of all suicides. Men aged 65 and older are four times more likely to commit suicide than men younger than 25. For women, the peak suicide rate occurs between 40 and 60 years of age, with rates declining gradually in the succeeding years.

Unfortunately, this common psychiatric disorder frequently goes unrecognized by primary care physicians. Although screening instruments have been found to be effective in identifying elderly depressed patients in the medical setting,[6,7] surveys suggest that as few as 25 percent of clinically significant depressions in medical patients are detected by nonpsychiatric physicians.[8] Detection of depression in the geriatric population can be particularly rewarding because treatment can frequently ameliorate or eliminate this disorder. In this paper we discuss the diagnosis and treatment of depression in the elderly.

The Clinical Diagnosis of Depression

The term "depression" is confusing because it may be applied equally to (1) a transient mood state in response to adverse events or (2) a persistent syndrome characterized by dysphoric mood and somatic symptoms that may be biologically determined. This single term is commonly applied to a continuum of feelings that ranges from unhappiness on one hand to a severe, life-threatening illness on the other. As a result of this varied use of the term "depression," psychiatric nosology has been marked by inconsistency and confusion in the past. The third edition of the *Diagnostic and Statistical Manual* (DSM-III)[9] attempts to standardize the diagnosis of this disorder by defining specific diagnostic criteria for a major depressive

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episode (see Table 1). Because DSM-III includes the somatic symptoms of depression (disturbances in sleep, appetite, psychomotor activity and energy level), these criteria resemble what has generally been called "endogenous" depression.

The characteristic signs and symptoms of depression in older adults can be divided into four general categories: mood, somatic, behavioral, and psychological. Depending on the patient, symptoms in these categories may range from mild to incapacitating. The mood changes typical of depression include obvious problems such as sadness and tearfulness. Such depressed feelings may be reflected in the patient's affect (observable emotions) by mournful, gloomy facial expressions or by blunted, constricted emotional tone. Other patients may complain less of sadness but will admit they no longer experience enjoyment and pleasure from daily activities. Some patients complain of mood changes characterized by anxiety, irritability, emotional lability or feelings of emptiness.

TABLE 1.—*DSM-III Diagnostic Criteria for Major Depressive Disorders*

Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable and worried. The disturbance must be prominent and relatively persistent but not necessarily the most dominant symptom. It does not include momentary shifts from one dysphoric mood to another—such as anxiety to depression to anger seen in states of acute psychotic turmoil.

The illness has had a duration of at least two weeks during which, for most of the time, at least four of the following symptoms have persisted and have been present to a significant degree.

- Poor appetite or significant weight loss (when not dieting); or increased appetite or significant weight gain.
- Insomnia or hypersomnia.
- Loss of energy, fatigability or tiredness.
- Psychomotor agitation or retardation (but not mere subjective feelings or restlessness or being slowed down).
- Loss of interest or pleasure in usual activities, or decrease in sexual drive (do not include if limited to a period when delusional or hallucinating).
- Feelings of self-reproach or excessive or inappropriate guilt (either may be delusional).
- Complaints or evidence of diminished ability to think or concentrate such as slowed thinking or indecisiveness (do not include if associated with obvious formal thought disorder).
- Suicidal ideation or wishes to be dead, or any suicide attempt.

Episode not superimposed on either schizophrenia, schizophreniform disorder or paranoid disorder.

None of the following predominate the clinical picture for more than three months after the onset of the depressive episode.

- Preoccupation with a mood-incongruent delusion or hallucination.
- Pronounced formal thought disorder.
- Bizarre or grossly disorganized behavior.

DMS-III = *Diagnostic and Statistical Manual*, third edition.[9]

The somatic signs and symptoms of depression may be the most common symptoms in older persons. Disruption of sleep, especially early morning awakening, is a distressing symptom for many older depressed patients. Other "vegetative symptoms" include anorexia with weight loss, fatigue, loss of libido and constipation. Older depressed patients commonly are somatically preoccupied and have multiple vague complaints of physical discomfort that appear to be unrelated to physical causes.

Behavioral changes, such as apathy, social withdrawal or loss of interest in previously pleasurable activities can be the first signs of depression in older patients. Patients with more severe depressions may have psychomotor retardation, slowing of speech and body movements, social withdrawal and (in severe cases) may refuse to eat or speak. Other patients may show psychomotor activation such as agitation, hand-wringing, obsessive worrying and restlessness. Those who feel irritable may behave in an angry or hostile manner towards family members or caretakers. Therefore, pronounced changes in a person's normal level of activity or behavior may indicate a depressive illness.

Elderly depressed persons experience a variety of psychological symptoms. Pessimism and hopelessness about the future as well as doubt that anything can be done to help them are often present. Some patients ruminate about past failures and consider themselves worthless and inadequate. Others complain bitterly about memory disturbances and poor concentration. Cognitive impairment such as disturbances of memory, attention and orientation, which are uncommon in young depressed patients, may be a prominent feature of late-onset depression. In fact, surveys suggest that older patients presenting to primary care physicians with complaints about their memory are more likely to have depression than dementia.[10] Such cognitive symptoms due to depression can result in an incorrect diagnosis of irreversible dementia. Severely depressed older patients may also exhibit bizarre delusions of

worthlessness, poverty or somatic dysfunction. Somatic delusions can take the form of believing, despite all evidence to the contrary, that bodily parts are cancerous or dead. Paranoia, particularly with delusions of persecution, is not uncommon in severe late-life depression. Such delusions frequently are associated with excessive concerns about guilt over real or imagined past failures, errors or indiscretions. Seriously depressed older patients may view any treatment efforts as futile and see the situation as hopeless and beyond assistance.

Differential Diagnosis of Depression

In severely depressed patients with sadness, agitation, pessimism, sleeplessness and depressed affect, clinicians generally have little trouble recognizing the disorder. However, for older patients with less severe forms of depression accurate recognition of the disorder may be problematic. In such patients, complaints of dysphoric mood may be absent or minimized. These patients instead focus on an array of somatic complaints rather than on the psychological or mood symptoms typical of depression. In fact, some elderly patients who appear depressed and who respond to antidepressants actually deny or do not experience a depressed mood state. Somatic preoccupations and multiple physical complaints may approach hypochondriasis. This excessive concern about the body may be one reason why older depressed persons are seen initially by an internist, family practitioner or surgeon. Hypochondriasis may serve an adaptive function by allowing the patient to seek medical treatment rather than psychiatric or emotional support. This shift in emphasis from the typical psychological and mood symptoms of depression toward somatic symptoms in an older depressed patient can be misleading to the clinician and makes the diagnosis of late-onset depression more difficult.

A clinician's attitude toward aging may also contribute to difficulties in recognizing depression in the elderly. Some clinicians are influenced by the common cultural biases about the aged, which regard depression, pessimism and apathy as normal consequences of growing older and, therefore, may not regard such problems as abnormal findings requiring therapeutic intervention. Such an attitude limits recognition of a potentially reversible clinical condition and delays or prevents valuably therapy.

The apathy, withdrawal, confusion and memory impairment that may accompany late-onset depression can easily be mistaken for dementia (so-called pseudodementia). However, unlike true dementia, these cognitive symptoms improve when the underlying depression is treated. Because such cognitive impairment is potentially reversible, it is especially important that clinicians recognize depression when present.

The increased frequency of medical disease in the elderly also complicates the differential diagnosis of depression. Some chronic illnesses are accompanied by symptoms that are similar to the "vegetative symptoms" of depression. Moreover, other illnesses actually produce clinical syndromes that are difficult to distinguish from a primary depressive illness. Both metabolic and endocrine disturbances can produce apathy, anorexia, malaise, decreased energy and somatic preoccupation that may be mistaken for depression. Table 2 lists common medical conditions that must be considered in the differential diagnosis of depression in older patients. The diagnostic assessment must also include careful consideration of the medications used by the elderly patient. The number of medications that adults take increases with age, and many drugs either exacerbate underlying depressive conditions or produce depression-

TABLE 2.—*Medical Illnesses Associated With Depressive Symptoms*

Metabolic/Endocrine
Hypoglycemia (iatrogenic), hypokalemia, hypercalcemia, uremia, hepatic failure, hypothroidism, hyperthyroidism (apathetic), hyperparathyroidism, Cushing's disease, Addison's disease.
Central Nervous System
Tumors and mass lesions, Parkinson's disease, multiple sclerosis, Alzheimer's disease, vascular disease.
Miscellaneous
Pernicious anemia, pancreatic carcinoma, metastatic carcinoma, systemic lupus erythematosus, infections, congestive heart failure, porphyria.

TABLE 3.—*Drugs Associated With Depressive Symptoms*

Antianxiety drugs
Barbiturates, benzodiazepines, meprobamate
Sedative hypnotics
Alcohol
Antipsychotics
Antihypertensives
Guanethidine, reserpine, methyldopa, clonidine, propranolol, diuretics
Digitalis
Corticosteroids
Estrogen preparations
Immunosuppressive and cytotoxic agents

like syndromes (Table 3). Because some older patients share drugs with friends, attention should not be limited solely to those drugs actually prescribed for the patient. Further, because prolonged alcohol abuse may be associated with depression, it is important to investigate the extent of recent alcohol use.

Treatment of Depression

Because of the interrelation of depression, physical illness and drug effects, the evaluation of depressed elderly patients should include physical, neurological and laboratory examinations. The last includes routine serum chemistries, thyroid function tests, analysis of urine, complete blood count, electrocardiogram and an x-ray study of the chest. The practice of cautiously reducing or even discontinuing all drugs that are not life-sustaining has merit and may produce dramatic clinical improvement. If a depressive episode is severe, or if significant medical problems complicate the diagnosis, evaluation within the hospital may be more appropriate than outpatient treatment. When depression is associated with pronounced anorexia, psychotic symptoms (such as delusions or hallucinations) or threatened suicide, the patient should be admitted to hospital for psychiatric examination.

If there is no medical or reversible cause for depressive-like symptoms and if symptoms are not so severe as to warrant admission to hospital, then outpatient treatment of depression is indicated. The selection of treatment should be based on the type of depression present. In general, the more acute, grief-like depression (commonly called situational depression) is short-lived, responds to environmental manipulation or interpersonal interaction and is not perceived as inappropriate by the patient or the family. Such depressions usually respond to supportive psychotherapy, counseling or environmental changes. Brief use of the benzodiazepines may relieve symptoms of anxiety or sleeplessness, but antidepressant medication is usually not required. This form of depression usually follows a clear, easily identified precipitant. More severe forms of depression (for example, so-called endogenous depression) are more pervasive and frequently result in multiple and more serious vegetative, behavioral and psychological symptoms. The endogenous depressive pattern is more commonly associated with anhedonia (inability to experience pleasure), which is frequently unresponsive to environmental changes. This form of depression may be associated with previous episodes of depression or a family history of depressive illness. Although both the situational and the endogenous depressive syndromes may be distressing to the patient, the latter tends to be prolonged and is more likely to interfere with normal functioning.

Regardless of the cause, older depressed patients can derive great benefits from psychotherapy or counseling. An empathic counselor who provides a supportive relationship that allows expression of sadness and exploration of losses can provide the older depressed patient with a valuable source of emotional support. The counselor must be careful not to allow his or her own discomfort about losses, commonly associated with aging, result in avoidance of these issues. For some patients with situational depression secondary to a specific major loss, a supportive interaction with one or a group of persons who have had the same experience is often helpful. For example, widow-to-widow counseling or talking to a group of patients who have also had myocardial infarctions can help the patient develop new coping skills, acquire a better perspective on his or her losses and work through the grieving process. The clinician can be helpful in suggesting that the patient contact suitable persons or groups.

Depressions that approximate the endogenous symptom pattern (gradual onset, prominent anhedonia and disturbances of sleep, appetite and psychomotor activity) are those most likely to respond to treatment with the tricyclic antidepressants (TCA).[11] Although few clinical studies of TCA in elderly populations have been reported, TCA are widely used and are effective in appropriately selected older patients.[12,13] There are a large number of tricyclic antidepressants available, but no single drug has been shown to be more effective than any other. However, the various antidepressants do have different side effects (Table 4). In the absence of a history of previous response to a particular TCA, the clinician should choose a drug with potential adverse effects most likely to be tolerated by the patient. For example, the sedating properties of doxepin or amitriptyline may be better tolerated by the agitated patient with a pronounced sleep disturbance. Similarly, the less anticholinergic TCA desipramine and nortriptyline may be better tolerated by older men with an increased susceptibility to the development of urinary obstructive symptoms due to prostatic enlargement. Patients with orthostatic hypotension

TABLE 4.—*Commonly Prescribed Tricyclic Antidepressants*

Tricyclic Antidepressant	*Trade Name*	*Usual Dose Range (mg/day)*		*Sedative Properties*	*Anticholinergic Properties*
		Young Adult	*Elderly*		
Tertiary amines					
Amitriptyline	Elavil	100-300	25-150	+++	++++
Imipramine	Tofranil	100-300	25-150	++	+++
Doxepin	Sinequan	100-300	25-150	+++	++++
Secondary amines					
Nortriptyline	Pamelor	50-100	10-60	+	+++
Desipramine	Norpramin	100-300	25-150	0	++
Protriptyline	Vivactil	20-60	5-30	0	+++

may better tolerate nortriptyline, which is reported to cause fewer changes in blood pressure.[14]

Regardless of the choice of an individual agent, starting doses of the TCA should be lower for elderly patients than those usually prescribed for younger adults[12] (see Table 4). Moreover, older persons, as a group, have a wider range of physical health symptoms, so that starting dosages need to be more individually determined for them than for younger patients. For example, the starting TCA dosage for a frail 80-year-old person may be 10 mg at bedtime, while a physically vigorous 65-year-old may tolerate a starting dosage of 50 mg. For most older patients in relatively good health, a reasonable starting dosage of the TCA (except for the more potent nortriptyline and protriptyline) is 25 to 50 mg at bedtime, which can be gradually increased in 25-mg increments at four- to five-day intervals until either a therapeutic effect is achieved, prohibitive side effects occur or the maximum dosage of the medication is reached. By starting the dosage low and gradually increasing the amount of drug given, side effects can be closely monitored, and patients will more likely tolerate the medication. When initiating treatment, it is important to talk with each patient and his or her family to provide support and reassurance. Both patient and family should be informed that the maximal therapeutic effect of the drug may require three or four weeks of treatment, although individual symptoms such as sleep disturbance or anxiety may respond more rapidly. When a therapeutic response is obtained, the dosage of the medication should be maintained for three to six months, then the amount of TCA can be tapered gradually and discontinued if symptoms do not recur. Clinicians should not provide suicidal patients with a large quantity of TCA because these agents are often lethal in an overdose.

The relationship between plasma levels of TCA and their therapeutic effect is not yet understood.[15,16] However, plasma TCA levels do indicate the extent of absorption of the drug and can be helpful to regulate the TCA dosage in patients who do not respond to the usual therapeutic dosage or who experience unusually severe adverse effects on low doses.

The elderly appear to be more sensitive to the adverse effects of tricyclic antidepressants.[12] These side effects include sedation, anticholinergic effects, signs of adrenergic hyperactivity (such as tremulousness and sweating) and cardiovascular effects. Because of anticholinergic side effects, these agents should be used cautiously in patients with narrow-angle glaucoma or urinary obstructive symptoms. Anticholinergic activity in the central nervous system may result in a delirium that is associated with increased lability of mood, increased agitation and disorientation. Postural hypotension can be a particularly bothersome cardiovascular side effect in older patients receiving TCA. Evidence suggests that substantial postural hypotension during TCA treatment can be predicted best by the degree of pretreatment hypotension.[17] Other cardiovascular effects of the TCA include a quinidine-like, membrane-stabilizing effect that may appear electrocardiographically as nonspecific ST-T changes and T wave flattening.[18,19] With increasing doses, cardiac conduction is progressively prolonged as reflected by increasing PR, QRS and QT interval prolongation. Because these agents tend to produce conduction disturbances, the TCA should be used cautiously in patients with evidence of preexisting conduction abnormalities or in patients receiving antiarrhythmic drugs with quinidine-like properties. The TCA also block the effects of guanethidine and antagonize the effects of clonidine, both used to treat hypertension in the elderly.

Although the TCA are commonly believed to be potentially cardiotoxic for the elderly, evidence

that imipramine is antiarrhythmic in therapeutic doses[13,14] indicates that this concern may have been overstated.[19] Furthermore, recently it has been shown that therapeutically effective doses of the TCA produced no significant effect on left ventricular pump function in depressed patients with well-defined heart disease.[13,20] It remains prudent, however, to avoid TCA use for two months following a myocardial infarction.[19]

In severely depressed patients who have delusions, TCA use alone is usually ineffective.[21,22] However, depressed patients suffering delusions often respond to treatment with a combination of antipsychotic agents and TCA.[23] Other possible treatments of depression in the elderly include monoamine oxidase inhibitors, electroconvulsive therapy and lithium.[12] All these treatments can be effective in appropriately selected patients; however, their use is best left to psychiatrists with experience in treating older persons.

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Diagnosis and Treatment of Dementia in the Aged

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Dementia affects an estimated 5 percent of the population 65 years of age and older, with 20 percent being affected at 75 years or older. Although the most common forms, primary degenerative and multi-infarct dementia, currently lack specific treatments, it is estimated that a thorough diagnostic evaluation will uncover a treatable cause in 10 percent to 20 percent. The differential diagnosis includes benign senescent forgetfulness, depression, adjustment disorder, paranoid states, amnestic syndrome, delirium, drug effects, systemic illnesses and intracranial conditions. The approach to each patient involves a history, physical examination, mental status evaluation and laboratory tests that focus on identifying treatable conditions. When no specific treatments are available, however, symptomatic treatments, including pharmacotherapy, environmental management, family supports and psychotherapy, can offer relief for both patients and their families and improve the daily functioning of the elderly patient with dementia.

DEMENTIA IS A nonspecific clinical syndrome with an organic cause characterized by global deterioration of intellect, cognition, behavior and emotions, without impairment of consciousness.[1] Of the 24 million persons 65 years of age and older in the United States today, about 3 million have acquired intellectual impairment sufficiently severe to warrant the diagnosis of dementia.[2-4] The estimated prevalence increases from about 5 percent at age 65 to 20 percent at age 80.[5,6] Usually, these patients suffer from dementias for which no specific treatments are available. There are, however, many causes for which specific treatments do exist, and the diagnosis of primary dementia should therefore not be made without sufficient evidence. For example, Smith and Kiloh[7] recently evaluated 200 patients admitted to a psychiatric hospital in Australia with the provisional diagnosis of dementia and reported that 13 of them (7 percent) had potentially reversible causes for this disorder; another 20 patients (10 percent) were found to have depressive pseudodementia. Although no large-scale epidemiologic studies have as yet determined the prevalence of reversible dementia in the aged, data from small samples suggest that

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ABBREVIATIONS USED IN TEXT

EEG = electroencephalogram
MSQ = Mental Status Questionnaire

10 percent to 20 percent of demented persons 65 years and older have potentially reversible disorders.[8-11]

Definition

Table 1 lists the diagnostic criteria for dementia, according to the third edition of the *Diagnostic and Statistical Manual* of the American Psychiatric Association *(DSM-III)*.[12] In summary, there are five criteria: (1) loss of intellectual ability resulting in social or occupational impairment, (2) memory impairment, (3) impairment in abstract thinking, judgment, other higher cortical functions or a personality change, (4) clear state of consciousness and (5) documented or presumed evidence of an organic cause. These criteria differ from earlier ones in several ways. First, the diagnosis is based on purely behavioral phenomena. Dementia, therefore, characterizes a clinical syndrome, a cluster of signs and symptoms which, in turn, must lead to a search for causative factors. Second, these criteria, unlike earlier ones, avoid reference to reversibility, duration and rate of onset. This departure from prior definitions may be a wise one. Reversibility and duration as criteria are difficult to apply because they can only be established retrospectively. Moreover, they are functions of knowledge current at any one time. Similarly, the rate of onset of illness as a criterion presents difficulties because not all dementias begin insidiously; for example, dementia due to anoxia may have an acute onset, yet may be clearly characterized by the *DSM-III* criteria.

Clinical Syndromes

Primary Degenerative Dementia

Primary degenerative dementia (Alzheimer's disease) accounts for an estimated 50 percent of the dementias of old age.[13] The illness generally has an insidious onset and occurs in women more frequently than in men.[14] The patient initially experiences varying degrees of memory loss, difficulty in learning new material, confusion and irritability. Later, disorientation, deterioration of personality and loss of ability to perform activities of daily living follow. As brain degeneration progresses, aphasia, agnosia and apraxia appear, along with severe deterioration of higher cognitive functions. Signs of cortical release are often prominent and can be demonstrated by the grasp, glabellar, palmomental, snout and sucking reflexes.[15] The end result of the dementing process is inanition and death, commonly from bronchopneumonia. Psychological responses include depression, suspiciousness, belligerence, paranoid ideas, agitation, hypochondriasis, anxiety, social withdrawal and emotional lability.

Several authors have reported family data on genetic influences in the development of this form of dementia.[16] Chromosome abnormalities, HLA (human leukocyte antigen) type and haptoglobins may also be important.[17] Slow virus, metals (such as aluminum) and neurotransmitter abnormalities have all been proposed as causative factors but definitive data are lacking.

Primary degenerative dementia is by no means limited to the "presenile" period of life. Both pathologically and clinically, the presenile and

TABLE 1.—*Diagnostic Criteria for Dementia**

- A loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning.
- Memory impairment.
- At least one of the following:
  (1) impairment of abstract thinking, as manifested by concrete interpretation of proverbs, inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks;
  (2) impaired judgment;
  (3) other disturbances of higher cortical function, such as aphasia (disorder of language due to brain dysfunction), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), "constructional difficulty" (for example, inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs),
  (4) personality change, such as alteration or accentuation of premorbid traits.
- State of consciousness not clouded (that is, does not meet the criteria for delirium or intoxication, although these may be superimposed).
- Either (1) or (2):
  (1) evidence from the history, physical examination or laboratory tests of a specific organic factor that is judged to be etiologically related to the disturbance, or
  (2) in the absence of such evidence, an organic factor necessary for the development of the syndrome can be presumed if conditions other than organic mental disorders have been reasonably excluded and if the behavioral change represents cognitive impairment in a variety of areas.

*From American Psychiatric Association.[12]

TABLE 2.—*Clinical Features of the Modified Hachinski Ischemia Score**

Feature	*Point Value*†
Abrupt onset	2
Stepwise deterioration	1
Somatic complaints	1
Emotional incontinence	1
History or presence of hypertension	1
History of strokes	2
Focal neurological symptoms	2
Focal neurological signs	2

*Adapted from Rosen WG et al.[23]
†A score of 4 or more is consistent with multi-infarct dementia.

senile forms of the illness are at present indistinguishable except by the age of onset—45 to 64 years for the presenile form and 65 or older for the senile type. The clinical diagnosis of either form remains one of exclusion.

Albert and co-workers[18,19] have described dementias in terms of cortical and subcortical disorders, and classify primary degenerative dementia as one of the cortical dementias. In contrast, subcortical dementias involve psychomotor retardation and include disorders associated with lesions of the subcortical structures, such as Huntington's disease, Parkinson's disease, progressive supranuclear palsy and multi-infarct dementia.

Multi-infarct Dementia

This form of dementia accounts for 25 percent to 40 percent of dementias for which no specific treatments are available.[13] Men are more often affected than women, and a genetic contribution has been suggested.[20] The earlier term "cerebral atherosclerosis" is now considered misleading because progressive involvement of cerebral arteries by atherosclerosis does not appear to lead to critical stenosis nor to produce mental impairment. Instead, multiple occlusions of small cerebral vessels result in widely distributed areas of microinfarction with concomitant mental impairment.[11] When it is the primary process, multi-infarct dementia can usually be differentiated by its sudden onset, focal neurological signs, frequent association with hypertension, emotional incontinence (for example, a patient having an angry outburst when confronted with a frustrating task) and stepwise decline in intellectual functioning (for example, a patient one day becomes apraxic; a week later aphasia suddenly develops).[21,22] The clinical signs and symptoms were codified by Hachinski and associates[22] in an ischemic score, which was recently modified by Rosen and co-workers (Table 2).[23] The higher the aggregate score, the more likely the diagnosis of multi-infarct dementia. Using the scale in conjunction with appropriate laboratory tests to rule out other causes of dementia increases accuracy in differentiating these two forms of primary dementia, although diagnostic rigor is impaired by the frequent coexistence of multi-infarct and primary degenerative dementia.

Parkinson's Disease

By the time dementia develops in association with Parkinson's disease, the diagnosis is obvious. We include it here as a reminder of the increased prevalence of dementia among these patients,

TABLE 3.—*Differential Diagnosis of Dementia*

- Benign senescent forgetfulness
- Depression
- Adjustment disorder
- Paranoid states
- Amnestic syndrome
- Delirium
- Drugs and toxins
  - Antidepressants
  - Lithium carbonate
  - Atropine and related compounds
  - Alcohol
  - Benzodiazepines
  - Barbiturates
  - Bromides
  - Phenytoin
  - Propranolol hydrochloride
  - Methyldopa
  - Clonidine
  - Mercury
  - Arsenic
  - Lead
  - Organophosphates
  - Carbon monoxide
- Systemic illnesses
  - *Metabolic*
    - Renal failure
    - Hyponatremia
    - Volume depletion
    - Hypoglycemia
    - Hyperglycemia
    - Hepatic failure
    - Hypothyroidism
    - Hyperthyroidism
    - Cushing's syndrome
    - Hypopituitarism
    - Hypoparathyroidism
    - Hyperparathyroidism
    - Addison's disease
    - Porphyria
    - Severe anemia
    - Hyperlipidemia
  - *Infections*
    - Meningitis
    - Tuberculosis
    - Endocarditis
    - General paresis
    - Pneumonia
    - Nephritis
    - Influenza
  - *Cardiovascular*
    - Congestive heart failure
    - Arrhythmia
    - Vascular occlusion
  - *Deficiency States*
    - Vitamin B_{12} deficiency
    - Folate deficiency
    - Pellagra
  - *Collagen Vascular Disorders*
    - Systemic lupus erythematosus
    - Temporal arteritis
    - Sarcoidosis
    - Behcet's syndrome
- Intracranial conditions
  - Normal-pressure hydrocephalus
  - Subdural hematoma
  - Brain abscess
  - Tumor
  - Stroke

TABLE 4.—*Examples of Different Types of Memory*

Memory Types	*Function*	*Tests*
Immediate ..	Attentiveness; ability to repeat new information	Ask patient to repeat a word or number
Recent	Ability to learn new information	Ask patient to remember a word and repeat it after five minutes
Remote	Ability to remember information known in the past	Ask patient to name place of birth or past presidents

which is estimated to range from 22 percent[24] to 40 percent.[25]

Rare Disorders

Pick's disease is a presenile dementia that resembles Alzheimer's disease clinically but differs morphologically in having no senile plaques or neurofibrillary tangles. Affecting primarily the frontal and temporal cortex, a frontal lobe syndrome (that may include impaired attention, inability to perform acts in sequence, inertia, perseveration and impulsivity) characterizes the illness in its early stages. Although some claim the differential diagnosis can be made postmortem only, others maintain that cerebral blood flow studies provide an acceptable in vivo measure.[26,27] *Creutzfeldt-Jakob disease,* another presenile dementia rare in the elderly, is believed to be caused by a slow virus infection. Familial cases may be due to such an infection superimposed on a genetically determined predisposition.[28] Clinically, it is characterized by generalized cognitive dysfunction that may be accompanied or preceded by fatigue, dizziness, apathy, irritability and confusion. Other symptoms include myoclonus, cerebellar ataxia, seizures, memory impairment and aphasia. Although *Huntington's disease* is typically accompanied by choreiform movements, the associated dementia may predate the movement disorder.[29] When these characteristic movements are absent, several features assist in identifying the disease, including autosomal dominant pattern of inheritance, age of onset usually in the mid-40's (but onset as late as 70 years has been reported),[30] prominent psychomotor retardation and loss of frontal lobe executive functions, such as problem-solving, planning and goal-directed behavior.

Differential Diagnosis

A wide variety of conditions can produce reversible dementia or clinical syndromes with a dementia-like picture. Table 3 lists many of these causes but is by no means a complete inventory. It is essential to first rule out the more common causes, such as drug effects, depression and physical illness. If pursuit of these proves unfruitful, a search for less common disorders should be undertaken, the sequence of procedures depending on the clinical circumstances of the individual case.

Benign Senescent Forgetfulness

As age progresses, memory declines to a certain degree in everyone. Impaired memory, though one of the hallmarks of aging, usually does not progress to produce the devastating deficits characteristic of dementia. Global deterioration of intellect, therefore, is not normal in the elderly. Kral[31] introduced the term "benign senescent forgetfulness" to differentiate certain age-related memory declines from the malignant process characteristic of dementia. In benign senescent forgetfulness, according to Kral, the patient has transiently impaired recall of relatively unimportant aspects of a remote experience (such as a place, date or name) but can remember and relate the essence of the experience.[32] Although Kral's specific criteria for discrimination have been criticized,[33] the concept is useful in sensitizing the clinician to different patterns of memory loss in the aged. Table 4 lists examples of different types of memory. The elderly have little difficulty in immediate memory; advancing age, however, coincides with substantial deficits in both recent and remote memory.[34] At the risk of oversimplifying, patients who forget where they put their glasses most likely have benign senescent forgetfulness, whereas patients who forget they wear glasses are more likely to have dementia. The elderly often benefit considerably when others help in their memory retrieval by repeating important information, or using checklists and other reminders.

Depression

The clinical presentation of depression in the elderly often mimics dementia, and this syndrome has been termed "pseudodementia."[35] (The subject of depression is discussed more fully in the article "Depression in Older Persons: Diagnosis and Management" by Barnes, Veith and Raskind elsewhere in this issue.) The frequency of mistak-

ing depressed for demented patients is estimated to range from less than 1 percent for cases admitted to a tertiary care referral system, to over 15 percent or 20 percent for cases in the community.[36,37] The apathy, psychomotor retardation, impaired concentration and occasional confusion in the depressed patient may readily be taken for dementia, particularly when accompanied by complaints of memory loss. And, complaints of memory loss are common in depression; unlike those in dementia, they tend to exceed by far the actual impairment of memory observed in psychological testing.[38] The patient with depressive pseudodementia also tends to answer questions with "I don't know" rather than give near-miss responses or avoid questions, as is characteristic of the demented patient. Furthermore, responses on cognitive testing are reported to be inconsistent. Wells describes pseudodementia as a "caricature or burlesque, not an imitation, of dementia"[39] (Table 5).

The differential diagnosis is complicated by the fact that dementia and depression often coexist. Depression frequently occurs as an early symptom of dementia and may be more prevalent in the multi-infarct than in the Alzheimer type of dementia.[40] If there is doubt about the diagnosis, a trial of antidepressant medication is indicated. Even when symptoms of depression are absent, such a clinical trial may assist in the differential diagnosis of masked depression and dementia. It may also help to reduce the functional impairment and, even without eliminating the underlying dementia, may enable the patient to function at a level compatible with community rather than institutional living.

Adjustment Disorder

With advancing age comes the increasing likelihood of loss. Bereavement due to death or moving away from friends and relatives, relocation, and other psychosocial or physiological stresses may impair mental functioning and result in the syndrome of dementia.[41] Even a brief hospitalization, where unfamiliar surroundings and other anxiety-provoking events disrupt the elderly patient's daily routine, can drastically alter cognition. Assessment of the patient's life situation, therefore, is essential in the evaluation. Reduction of stress often clears up the mental deficit or, in the case of a mild preexisting dementia, permits the person to return to his or her previous level of functioning.[42]

Paranoid States

An estimated 10 percent of persons admitted to psychiatric hospitals after the age of 60 suffer from schizophrenia-like conditions arising for the first time late in life.[43] Among community resi-

TABLE 5.—*Clinical Features of Pseudodementia and True Dementia**

	Pseudodementia	*Dementia*
Duration of symptoms before physician consulted	Short	Long
Onset can be dated with some precision	Usual	Unusual
Family aware of dysfunction and severity	Usual	Variable† (rare in early stages, usual in late stages)
Rapid progression of symptoms	Usual	Unusual
History of prior psychopathology	Usual	Unusual
Patient's complaints of cognitive loss	Emphasized	Variable† (minimized in later stages)
Patient's description of cognitive loss	Detailed	Vague
Patient's disability	Emphasized	Variable† (concealed in later stages)
Patient's valuation of accomplishments	Minimized	Variable†
Patient's efforts in attempting to perform tasks	Small	Great
Patient's efforts to cope with dysfunction	Minimal	Maximal
Patient's emotional reaction	Great distress	Variable† (unconcerned in later stages)
Patient's affect	Depressed	Labile, blunted or depressed
Loss of social skills	Early	Late
Behavior congruent with severity of cognitive loss	Unusual	Usual
Attention and concentration	Often good	Often poor
"Don't know" answers	Usual	Unusual
"Near miss" answers	Unusual	Variable† (usual in later stages)
Memory loss for recent versus remote events	About equal	Greater
Specific memory gaps ("patchy memory loss")	Usual	Unusual
Performance on tasks of similar difficulty	Variable	Consistent

*Adapted from Wells CE: The differential diagnosis of psychiatric disorders in the elderly. *In* Cole JO, Barrett JE (Eds): Psychopathology in the Aged. New York, Raven Press, 1980

†Wells lists the characteristics of the later stages. In our clinical experience these manifestations are variable early in the course of dementia and are helpful in the differential diagnosis only if they are in the direction seen in later stages of dementia.

dents, the frequency is only 1 percent to 2 percent.[44] Overt psychotic symptoms often occur after a prolonged prodromal period of increased social withdrawal, suspiciousness and eccentric behavior. According to Post,[45] the typical patient is an elderly woman living alone who develops the belief that others interfere with her property. She claims they displace objects in her home, sometimes steal them, and that they talk about getting rid of her within her earshot. Many of these paranoid elderly manage to get by in their communities. Some become so disturbing to neighbors that they are finally referred to psychiatrists.

The paranoid symptoms that often accompany dementia can be mistaken for schizophrenia. Underlying dementia may thus be overlooked and inadequately diagnosed and treated. Conversely, patients who present with symptoms and signs of dementia accompanied by paranoid symptoms may, in fact, not have dementia but rather schizophrenia or another treatable paranoid disorder that often has a good prognosis if treated appropriately with neuroleptic medication.

Amnestic Syndrome

The essential feature of the amnestic syndrome is impairment of recent memory in a clear state of consciousness. Immediate memory is preserved, but the ability to learn new material is defective. For example, such patients cannot learn and remember the name of their hospital or physician, but can repeat a word or number. Although usually caused by thiamine deficiency associated with alcohol abuse, anything that can damage the diencephalic and medial temporal structures of the brain (for example, anoxia or head trauma) can cause the amnestic syndrome. Patients with this disorder often have a shallow affect, although they may appear superficially friendly and agreeable. The patient tends to fill in memory gaps with imaginary events through confabulation. Intact immediate memory and the absence of global intellectual impairment differentiates amnestic syndrome from dementia.

Delirium

Both delirium and dementia involve disturbances in cognitive functioning and thus can be confused clinically. Moreover, elderly patients with preexisting dementia are not protected against the development of delirium; in fact, the two conditions frequently coexist.[46-48] Lipowski[48] has reviewed differences in some of the essential features of delirium and dementia in the elderly: The course of delirium tends to be one of acute onset, often at night, lasting from days to weeks, while that of dementia is usually one of gradual onset with a duration of at least a month (*DSM-III* does not include this distinction[12]). Impairment of attention, alertness and perception invariably occurs in delirium and tends to fluctuate, typically with nocturnal exacerbation and lucid intervals. Dementia, on the other hand, presents without disturbance of consciousness, while perception and alertness, if abnormal, tend to remain relatively stable over time. Lipowski emphasizes that the presence of delirium in patients known or thought to have dementia requires a search for underlying causes because there is no evidence that primary degenerative dementia can cause delirium in the absence of additional causative factors. Even though patients who survive delirium have a high probability of escaping residual mental impairment, brain damage may occur as a result of the underlying cause of the delirium.

Drug Effects

Drugs deserve special emphasis in the cause of dementia in the aged. The use of various drugs by this population is pervasive, owing in part to the increased prevalence of illness of all kinds in the upper age groups. Chien and colleagues[49] surveyed 242 elderly persons living in a community in New York State. They found that these patients used a total of 301 types of medication (60 percent by prescription), with 83 percent of them taking 2 to 6 drugs each and 14 percent of them taking 7 to 15 drugs each. In addition, 14 percent of the total misused their medications because of misunderstanding of drug indications. Similar extensive use of single and multiple drug regimens among the elderly have been documented in multicenter studies in this country[50] and in Great Britain.[51] Medications tend to cause toxic effects in the elderly because of age-related changes in body function and pharmacokinetics.[52] These changes include prolonged half-life of drug, inconsistent alterations in the volume of distribution, reduced serum albumin levels resulting in occasional increases in unbound circulating drug, and decreased renal clearance.[53]

Neuroleptic and hypnotic agents, antidepressants and sedatives, used widely in the elderly,[54] may be among the most frequent causes of drug-related treatable dementia. Numerous other drugs, including digitalis preparations, propranolol and

antihypertensive agents, have also been implicated.[55] The confusion of digitalis intoxication may be readily misdiagnosed as dementia; diuretics, producing weakness and fatigue as a result of potassium depletion, may lead to a mistaken diagnosis of primary dementia, especially in the presence of mental confusion. Alcohol abuse occurs in the elderly as well as the young and may be a cause of treatable dementia often overlooked.[37] Schuckit and associates[56] reported the prevalence of alcoholism to range from 2 percent to 10 percent, the higher rates among widowers and medical patients.

Systemic Illnesses

An elderly person's brain is extremely sensitive to changes in its environment, and almost any systemic illness can effect such a change and produce dementia. Table 3 lists some of the more common conditions that can present as dementia. Many of these illnesses can also appear as delirium, but the overlap is not absolute. For example, hypernatremia has been reported as a cause of delirium but not dementia.[11] Disorders of thyroid metabolism are the most frequent endocrinopathies that cause dementia, and both hypothyroidism and apathetic hyperthyroidism must be considered in an elderly patient with symptoms of dementia. Other common conditions include anemias due to folic acid or vitamin B_{12} deficiency, uremia and, of course, electrolyte disturbances, particularly with the prevalence of diuretic use in the aged. Postoperative confusional states due to many mechanisms, such as low blood volume, hypoxia and sensory deprivation, are also important to keep in mind.

Malnutrition is not limited to alcohol abusers and in itself has been linked to cognitive impairment.[57] Although low income and poor health are more closely related to malnutrition than age per se,[58] many factors predispose older people to dietary inadequacies. These include financial problems, physical limitations (such as inadequate dentures) and psychological stresses (such as loneliness, bereavement or depression).

Intracranial Conditions

When recognized early enough, subdural hematomas, certain tumors (especially meningiomas) and central nervous system infections (including brain abscess, meningitis and neurosyphilis) are among the treatable causes of dementia. Postictal confusional states could conceivably present as dementia, although delirium would be the more likely appearance. The triad of gait disturbance, incontinence and dementia suggests the diagnosis of normal-pressure hydrocephalus. The current treatment of this disorder—shunting of cerebrospinal fluid[59,60]—has been open to question because of the high risk-to-benefit ratio of this procedure.[61]

Approach to Patients

History and Physical Examination

A detailed history is essential in the comprehensive evaluation of the mentally impaired patient. Because of the patient's impairment, the physician needs access to someone who knows the patient well and who can validate and supplement the information obtained from the patient. The onset of symptoms should be carefully explored with an attempt to distinguish acute from insidious onset. This distinction may be difficult to make because a traumatic event (such as retirement, bereavement or illness) may produce a considerable worsening of previously unrecognized insidious intellectual decline. Given the profound effect that medications can have on the mental status of geriatric patients, an inventory of both prescription and over-the-counter drugs is also of utmost importance.

A thorough physical examination and careful assessment of neurological status will help to identify underlying medical conditions. Illnesses ranging from myocardial infarction to Cushing's syndrome can present initially with confusion as the primary symptom.[62] Physical examination often provides pathognomonic information. Asterixis screens for not only diseases of the liver but also a variety of metabolic diseases.[11] Too frequently neglected is the question of adequate sensory input. Elderly patients may appear confused or apathetic mainly because they have inadequate sensory input, and inappropriate answers to questions may result from a patient's embarrassment about disclosing a hearing impairment.

Mental Status Examination

Because dementia represents a defect in cognition, the mental status examination should focus on memory, retention and recall of new information, the ability to calculate and the quality of judgment, as well as the patient's emotional state. The physician can evaluate these functions by paying close attention to the patient's verbal and

nonverbal communications throughout the interview. The intellectually impaired elderly patient should be approached with full regard for his or her sense of dignity and wish to appear competent. Formal testing to confirm or invalidate the diagnosis of dementia can often be done subtly, in such a manner as not to insult the patient. Although such testing is best spread throughout the interview, standardized brief mental status questionnaires[63-67] are often useful in quantifying the patient's cognitive state, especially for serial examinations aimed at following improvement or decline.

The Mental Status Questionnaire (MSQ)[63] is one scale used widely throughout the country (Table 6). The test consists of ten questions and takes five to ten minutes to perform. The results of the MSQ provide a numerical score, ranging from 0 to 10, that estimates the degree of brain dysfunction. Isaacs and Kennie[68] have introduced another simple instrument used extensively in geriatrics, the set test. This test asks the patient to name ten items in each of four general categories such as towns, colors, animals and fruits. For each different item named, the patient scores one point. A total of less than 15 of the possible 40 points indicates dementia. Scores from 15 to 24 are suggestive of dementia.

The Face-Hand Test (FHT), used together with the MSQ, has been found to provide excellent diagnostic differentiation between patients suffering from general cerebral dysfunction and those without such disorders.[69] Briefly, the examiner performs two series of double simultaneous stimulations, consisting of ten trials each, one with the patient's eyes closed and the other with eyes open (Table 7). Extinction or extinguishment is the most common error and refers to one of the two stimuli not being perceived, nearly always the one applied to the hand. The second most common error and one indicating more serious pathology is that of displacement. Errors made on symmetrical stimuli (trials 5 and 6) indicate that the subject has an impairment of sensory modalities or is not able to follow instructions. The cutoff criterion indicating brain dysfunction is any error made after trial 6 in the eyes-closed series, though a person who makes errors with eyes open generally has a more severe disorder. Again, tests such as the FHT are useful primarily in alerting

TABLE 6.—*The Mental Status Questionnaire for Evaluation of Brain Dysfunction in the Aged**

Questions	*Answer Interpretation*	
1. Where are you now? (Name and kind of place)	*Total Incorrect Answers Including Unanswered Questions:*	*Estimate of Degree of Brain Dysfunction:*
2. Where is this place? (Address)	0-2 Incorrect	None or mild
3. What month is it? } What is the date?	3-8 Incorrect	Moderate
4. What year is it? } What is the date?	9-10 Incorrect	Severe
5. What day of the month is it? } What is the date? (Correct if within two days)		
6. How old are you? (Age in years)		
7. What month were you born? } When were you born?		
8. What year were you born? } When were you born?		
9. Who is President of the United States?		
10. Who was President before him/her?		

*Adapted from Kahn RL: Psychological aspects of aging, *In* Rossman I (Ed): Clinical Geriatrics. Philadelphia, J. B. Lippincott Co, 1971, pp 107-113

TABLE 7.—*The Face-Hand Test—Examples of Response Errors in Brain Dysfunction**

Trial	*Stimulus Pair*	*Response*	*Type of Error*
1	Right cheek-left hand	Both cheeks	Displacement
2	Left cheek-right hand	Left cheek, right arm	Displacement
3	Right cheek-right hand	Right cheek only	Extinction
4	Left cheek-left hand	Left cheek only	Extinction
5	Right cheek-left cheek	Both cheeks	(Correct)
6	Right hand-left hand	Both hands	(Correct)
7	Right cheek-left hand	Right cheek only	Extinction
8	Left cheek-right hand	Both cheeks	Displacement
9	Right cheek-right hand	Right cheek only	Extinction
10	Left cheek-left hand	Left cheek, left arm	Displacement

*Adapted from Fink M, Green M, Bender MB: The Face-Hand Test as a diagnostic sign of organic mental syndrome. Neurology 2:46-58, 1952

the physician to the existence of cognitive impairment. Once alerted, the physician can proceed with the required workup.

More extensive neuropsychological assessment can at times aid in diagnosis, particularly when there is a need to distinguish dementia from functional psychiatric disorder.[70] Recent studies by La Rue and Jarvik[71] suggest that long-term records of cognitive function may be particularly useful and may predict the development of primary dementia 20 years before the symptoms are recognized clinically.

Laboratory Examinations

Laboratory tests should be obtained as indicated by the history and examinations, giving highest priority to the diagnosis of treatable dementia. The actual number and order of tests depend on the particular case presentation and the physician's clinical judgment. Fox and coworkers[9] evaluated 40 patients 63 years of age and older using a series of laboratory tests, which they termed a dementia protocol (Table 8); the tests uncovered potentially treatable dementia in five of the patients. The protocol showed many laboratory abnormalities not directly related to dementia but rather to ongoing systemic disorders; adequate treatment of these disorders, however, often resulted in improvement of the dementia. Table 9 lists the minimum screening tests for evaluating dementia recommended by the Task Force sponsored by the National Institute on Aging.[11]

Evidence of cortical atrophy on a computed tomographic (CT) scan relates more to age than to degree of dementia.[72-75] Accordingly, the CT scan is used primarily to rule out such intracranial conditions as space-occupying lesions, hydrocephalus, hemorrhage, infarction and brain edema.

The electroencephalogram (EEG) may be helpful in determining whether there is, in fact, organic disease present, whether it is focal or diffuse, and, by serial study, whether the process is stable, progressing or resolving.[76] Slight slowing of the EEG frequencies is common in healthy elderly persons,[76,77] but in primary degenerative dementia, the EEG is frequently abnormal with generalized slowing, the severity of which is reported to correlate with the degree of functional impairment.[76,78,79] It should be emphasized, however, that the EEG may be normal in dementia, particularly in the early stages of the disease.[80-82]

Although laboratory investigations are essential in the diagnostic workup of dementia, no one test or combination of tests offers a definitive diagnosis for primary dementia. Instead, they aid in excluding other conditions or else are still experimental.

Treatment

Specific Treatments

As in the treatment of any disease, the initial step involves accurate diagnosis. Specific treatment of the underlying cause may not reverse the cognitive deficit completely, but it will arrest the dementing process and often alleviate the associated symptoms. A complicating factor in treating

TABLE 8.—*Results of Dementia Protocol Laboratory and X-ray Studies in 40 Patients with Provisional Diagnosis of Dementia**

Laboratory Test	*Frequency of Abnormal Results*	*Frequency of Abnormal Results Leading to Diagnosis of Potentially Treatable Illness*†
Hemoglobin	12	1
Mean corpuscular volume	5	1
Erythrocyte sedimentation rate	13	..
Electrolytes	2	..
Calcium	2	..
Blood urea nitrogen	8	..
Fasting blood glucose level	10	..
Liver function tests	10	..
Protein electrophoresis	0	..
Serum vitamin B_{12} levels	0	..
Serum folic acid	1	..
T_4 level	2	2
Skull x-rays	6	..
Electroencephalogram	34	1
Brain scan and nuclide angiogram	9	1
Cerebrospinal protein	14	3
Computed tomographic scan	4	1

*Adapted from Fox JH, et al.[9]
†N = 5 patients

TABLE 9.—*Screening Tests for Evaluating Dementia**

1. Complete blood count with sedimentation rate
2. Analysis of urine
3. Stool examination for occult blood
4. Serum urea nitrogen and glucose; serum electrolytes (sodium, potassium, carbon dioxide content, chloride, calcium, phosphorus); bilirubin; serum vitamin B_{12}, folic acid
5. Tests for thyroid function
6. Serological test for syphilis
7. Roentgenogram of the chest
8. Electrocardiogram
9. Computerized tomography (CT scan) of the brain

*Recommended by the Task Force sponsored by the National Institute on Aging.

older patients is that they rarely suffer from a single disease, so that the treatment of one illness often affects other concurrent illnesses or treatments. For example, treating hypertension with methyldopa in a patient with multi-infarct dementia may worsen a concurrent depression or further reduce cerebral blood flow, thus risking recurrent infarction. Even minor medical illness can upset a delicately maintained intellectual integrity. Elderly patients with dementia are especially vulnerable to such complications as falls, bed sores, fecal impactions and incontinence. Meticulous hygiene and treatment of multiple medical conditions are essential for optimizing remaining intellectual abilities. For most elderly patients with dementia, no specific treatment is available. Though the prognosis is bleak, the comfort and daily functioning of these patients can be improved considerably through the use of symptomatic treatments.

Pharmacological Treatments

The elderly frequently complain of insomnia because with advancing age the time required for sleep onset increases. The problem is even more severe for the elderly with dementia.[83] If chloral hydrate is ineffective, then a short-acting benzodiazepine, such as lorazepam, ½ to 1 mg several hours before bedtime, often relieves early insomnia and avoids the paradoxical excitement more commonly experienced with the barbiturates. Benzodiazepines with longer half-lives (for example, diazepam) should be avoided because of a tendency to accumulate in the blood. The sedative action of any of the antianxiety agents can increase withdrawal, aggravate cognitive deficits, cause confusion and worsen depressive symptoms in an elderly patient with dementia, and so must be used with caution.

Neuroleptic agents are indicated for the treatment of the agitation and paranoid symptoms that frequently accompany cognitive deficits in the aged. Low doses of a high-potency neuroleptic drug—for example, a dosage of ½, 1 or 2 mg per day of haloperidol or the equivalent dose of another neuroleptic, can be given several times a day (in divided doses) or as one dose in the early evening. Early evening doses seem to lessen daytime sedation and decrease "sundowning" (worsening agitation and confusion at night). Low-potency neuroleptic agents such as thioridazine or chlorpromazine are more likely to cause postural hypotension and tachycardia, which can be dangerous in the elderly, especially in those with already compromised cardiac status.

Antidepressants are useful for the treatment of depressive symptoms (particularly insomnia) occurring in patients with dementia, aside from the therapeutic trial of antidepressants indicated when pseudodementia is suspected. Side effects can be minimized by using lower dosages that are increased gradually, such as 25-mg increments of doxepin or desipramine, which are increased every few days. Daily dosages necessary for a therapeutic effect can range from as low as 25 mg to more than 150 mg but rarely as high as 200 mg. Giving the drug in divided doses throughout the day lessens the common side effects of postural hypotension and anticholinergic symptoms (such as dry mouth or urinary retention). All tricyclic drugs, except perhaps doxepin, appear to prolong both atrial and ventricular depolarization, an important consideration when treating patients with concurrent disease of cardiac conduction.[84] A wide variety of investigational compounds have been studied and many have been used clinically. As yet, pharmacologic efforts to increase intellectual functioning have been disappointing. Case reports of the efficacy of cerebral vasodilators often fail tests of replication and double-blind study design.

Hydergine (dihydrogenated ergot alkaloids), not primarily a cerebral vasodilator, has offered some promise in improving mood and self-care.[85] These improvements, however, have been inconsistent and of questionable clinical significance.[86] Another approach has been to enhance cholinergic activity in the brain. Autopsies on subjects with primary degenerative dementia have demonstrated a reduction in choline acetyltransferase, which is consistent with central cholinergic deficit.[87,88] Furthermore, preliminary trials of cholinergic agonists have improved memory in young and old normal volunteers.[89-91] However, trials of these agents, including physostigmine,[92,93] choline[94] and lecithin,[95] have shown no effect on memory in patients with dementia.

The psychostimulant methylphenidate has been reported to cause global improvement in elderly patients with depression and cognitive impairment,[96,97] although these reports have been criticized on methodological grounds.[98,99] A possible justification for the use of psychostimulants lies in the recent work of Bondareff and associates,[100] which showed a deficiency of noradrenergic cells in patients with primary degenerative dementia. A

recent well-controlled trial suggests that improvement of apathy and withdrawal results from treatment of underlying depression rather than treatment of cognitive impairment per se.[101] Experiments with animals in which neuropeptides (adrenocorticotropic hormone [ACTH]-analogues) were used have shown some promise in enhancing mental functioning.[102] DeWied and co-workers[103] maintain that ACTH and its analogues have short-term effects on arousal and attention. So far, neither peripheral endocrine effects nor improved intellectual functioning have been detected in humans. Other agents and treatments under investigation but not yet shown to be effective include procaine hydrochloride, piracetam, and hyperbaric oxygen.[104,105]

Environmental Management

The sensitivity of intellectually impaired elderly patients to their surroundings requires optimal stimulation. Too much or too little environmental stimulation may result in withdrawal or agitation. Either of these results, when extreme, can make the difference between institutional care and functioning in the community.

Patients with dementia do best in familiar and constant surroundings. Daily routines increase their sense of security. Prominent displays of clocks and calendars, nightlights, checklists and diaries all aid in their orientation and memory. Medication schedules must be kept as simple as possible. Moves should be avoided, but, if necessary, photographs and other familiar objects from the patient's previous home should be placed nearby in an effort to create a home-like environment. Frequent family visitors and access to current events through newspapers, radio and television are also important to maintain the patient's awareness of the environment.

Family Support

Another essential aspect of management is support for and from family members. Education and counseling about the nature of the patient's illness, from the beginning, encourages family involvement in the patient's treatment. Uninformed relatives may react with anger and puzzlement to the emotional lability characteristic of so many demented patients. The patient's loss of inhibitions, emotional and verbal, as well as physical incontinence, may cause embarrassment to the family and be misinterpreted as willful behavior demonstrating lack of love or concern.

Psychotherapy

Both patient and family often benefit from psychotherapy. The physician can provide information about the nature of the illness and about ways to cope with intellectual deficits. Patients often need help in grieving and accepting their disability as well as support in maximizing remaining abilities and adaptive skills. Psychological support for caretaking persons will lighten their emotional burden. Anger, guilt, frustration and helplessness are all natural responses to the task of caring for a once vital and now deteriorating loved one. The relatives often need reassurance that such reactions are common and that discussing them can offer some relief.

Conclusions

Dementia, then, is not part of normal aging. Some 80 percent to 95 percent of persons 65 years and older never become demented. When dementia develops, therefore, physicians must pursue an adequate differential diagnosis and focus on a search for treatable disorders. In fact, a treatable cause will be found in 10 percent to 20 percent of cases. Even though the most frequent types of dementia, primary degenerative and multi-infarct dementia, have no specific treatments, palliative measures and symptomatic management can ameliorate the suffering of both patients and their families.

Dementia is defined with regards to a person's intellectual, social and occupational functioning, and the patient with dementia generally demonstrates a graduated decrement in these faculties. The physician can maximize the patient's functioning through not only medical and pharmacological interventions but also through environmental management and support of the patient's family. The goal is to help the patient when such help is needed, but not to take away opportunities for self-care when limited self-care is possible.

There is probably no experience as desperate as hearing that nothing can be done to stop the process. In this respect, dementia resembles cancer but usually runs a longer course; reports of dementias lasting 20 years are not unusual. The demented patient, moreover, is more helpless than the cancer patient when unable to participate in in his or her own treatment decisions, and too often the able patient is not consulted. Even the most severely demented patient maintains some awareness of the environment, and this usually

includes awareness of cognitive deficits. The prevalence and degree of suffering of both patients and their families attest to the need for conscientious and humane treatment while awaiting results of research that will provide more effective therapies for this devastating illness.

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Urinary Incontinence in the Elderly

JOSEPH G. OUSLANDER, MD, *Los Angeles*

Urinary incontinence is a common and distressing problem for elderly patients, their families and friends, and the health professionals who care for them. It is a heterogeneous condition, and appropriate management depends on a thorough evaluation and understanding of the multiple factors that can play a role in its cause and perpetuation. Identifying reversible causes of transient incontinence, and appropriate management of incontinence that is associated with acute illness, can be important in preventing the problem from becoming established.

A thorough diagnostic evaluation of urinary incontinence in the elderly, and appropriate use of the different types of therapy, will greatly improve the management in these cases. The need and opportunities for research to improve the management of incontinent elderly persons should be considered by all those involved in caring for this population.

> *. . . a patch of urine cannot be readily explained—its treatment has proved beyond most of us; and as to its significance, it will make the difference between social acceptance and rejection with all that involves in prolonged hospital care and expense.*
>
> J. L. NEWMAN
> "Old Folks in Wet Beds"
> *British Medical Journal,* 1962

ALTHOUGH THESE FEW PHRASES were written 20 years ago, they aptly summarize the essence of what remains a major problem in the care of the elderly.

Incontinence of urine is a common and frequently incapacitating condition that afflicts nearly 3 million elderly people in this country, and millions of others throughout the rest of the world. It has substantial impact on a person's well-being, on the ability of family or friends to cope with an old person and on the costs of health care for this population.

Despite the heterogeneous causes of urinary incontinence in the elderly, and the dearth of well-designed research on its management, several basic principles regarding the cause, diagnosis and treatment of this condition can serve to greatly improve its overall management.

It is the purpose of this article to briefly review these basic principles, and to provide a rational approach to elderly incontinent patients. Directions for future research will be suggested that could lead to even better understanding and approaches to the management of this condition.

Defining the Problem

Prevalence

Studies in Great Britain and Europe have found the prevalence of urinary incontinence in older

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patients in hospitals to be between 18 percent[1] and 40 percent[2] in men, and 24 percent[3] and 46 percent[2] in women. In elderly persons living in the community the prevalence has ranged from 5 percent[4] to 25 percent[5] in men, and from 7 percent[4] to 42 percent[5] in women. In the United States, between 28 percent[6] and 50 percent[7] of the elderly in nursing homes are incontinent.

There are several reasons these prevalence figures are so varied—including whether the study was done in the community or institutions, the timing of the study in relation to acute illness, and how the investigators defined incontinence and asked about the problem.

Because urinary incontinence is such a heterogeneous condition, a precise definition is important for studying the problem systematically. It is probably best to define incontinence in a general way (such as "any uncontrolled leakage of urine at any time") and to develop a classification based on its severity, using the number of incontinent episodes per day, or even measuring the amount of urine by weighing soiled underclothes.[8]

In a recent British survey, which more precisely defined incontinence and included older persons in the community as well as in institutions, 11 percent of men and 17 percent of women were found to have some problem with urinary incontinence.[9]

Whatever the precise prevalence, it is clear that millions of elderly persons throughout the world are afflicted with this condition, and many more probably suffer with it while failing to admit its presence.

Factors Associated With Incontinence

There is very little information characterizing those with this disorder. Factors that may have important implications for prevention, prognosis and management remain to be defined.

A relation between urinary incontinence and cognitive impairment has been recognized in a few studies,[2,9] but this was in older patients in institutions, where the prevalence of cognitive impairment approaches 50 percent; the importance of this information alone is therefore uncertain. Most of the elderly seen at one outpatient incontinence clinic in Great Britain did not have substantial cognitive impairment and also could walk without assistance,[10] but the important relationship between these characteristics and the severity of the incontinence was not described.

One important factor associated with incontinence in the elderly is acute illness. Previously continent older persons often become incontinent when admitted to hospital for a variety of acute conditions.[11] This relationship may explain the transience of urinary incontinence in up to a third of such persons in some studies.[9,11]

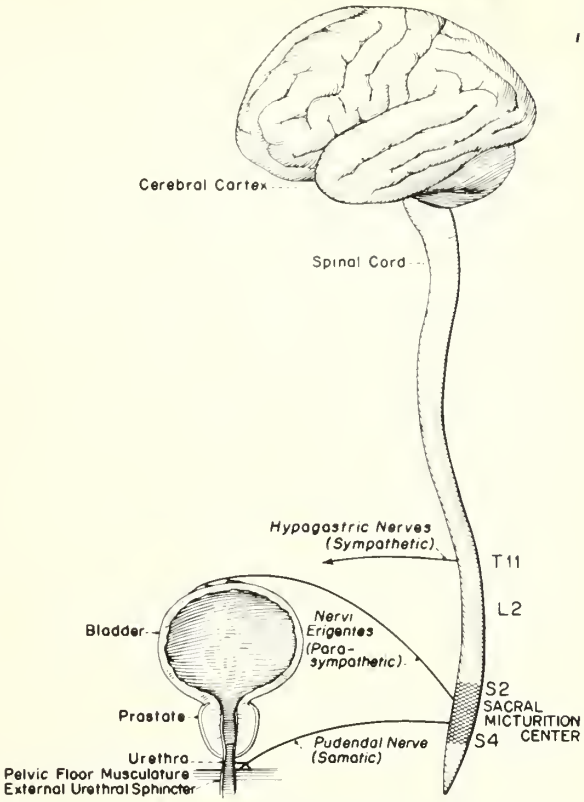

Figure 1.—The structural components of normal micturition.

The relationship between acute illness and incontinence is important because appropriate management of the incontinence during this period of acute illness may prevent a transient problem from becoming established, with attendant complications.

Complications of Incontinence

There are a myriad of medical, psychosocial and economic complications of urinary incontinence.

Those in whom this problem develops tend to withdraw from social activities, become isolated and frequently depressed. Their families and friends often have more difficulty dealing with incontinence than any other caretaker function. For these reasons, incontinence is a major factor predisposing the elderly to institutional admission.

Once present, incontinence and its management

give rise to several medical complications. These include decubitus and other skin ulcerations (especially recurrent ballanitis from external catheters) and recurrent urinary infections, as well as a higher risk for sepsis and death.

Precise information on the costs of caring for the elderly incontinent persons is not available. It has been estimated that as much as a third of the cost of nursing home care in Great Britain is accounted for by the management of incontinence.[12] Similarities in prevalence, as well as the increasing costs of supplies, nursing care and laundry, suggest that the management of incontinence accounts for a substantial portion of the $18 billion a year spent on nursing home care in this country.*

TABLE 1.—*Causes of Urinary Incontinence in the Elderly*

- Basic causes of incontinence
  - Urological
  - Neurological
  - Locomotor
  - Psychological
- Cause of transient incontinence
  - Urinary tract infection
  - Acute illness—especially when accompanied by:
    - Fatigue
    - Immobilization
    - Hospital admission and environmental barriers
    - Confusion
  - Other acute confusional disorders
  - Retention with overflow incontinence
    - Fecal impaction
    - Anticholinergic drugs
    - Spinal cord compression
  - Drugs
    - With effects on the autonomic nervous system
    - Sedatives and tranquilizers
  - Psychological
    - Depression with regression and dependency
    - Hostility
- Causes of established incontinence
  - Previous surgical operation
    - With damage to sphincters or pelvic innervation
  - Diseases of the cerebral cortex
    - Stroke
    - Dementia
    - Parkinson's disease
  - Diseases of the spinal cord
    - Compression by tumor, spondylosis, herniated disc
    - Trauma
    - Demyelination
  - Retention with overflow
    - Atonic bladder due to diabetes, alcoholism
    - Prostatic obstruction
    - Urethral stricture
  - Diseases of the bladder
    - Chronic cystitis
    - Carcinoma
    - Calculi
  - Uninhibited bladder
  - Stress incontinence

Causes of Urinary Incontinence in the Elderly

Normal Micturition

It is important to briefly review the basic anatomy and physiology of micturition to understand the pathophysiology of incontinence.

Micturition is a complex, dynamic process that involves the coordination of several components. Figure 1 depicts the structures that are involved in the process of micturition.

Micturition is basically controlled by the sacral micturition center (S2-4) of the spinal cord. This center receives sensory input from the bladder and surrounding structures, and sends motor input to the bladder via the nervi erigentes (parasympathetic, cholinergic) and to the urethral sphincter via the pudendal nerve (somatic). These structures also receive sympathetic input from the hypogastric plexus; α-adrenergic stimulation contracts the external sphincter, and β-adrenergic stimulation relaxes the bladder as it fills, and relaxes the bladder outlet during micturition.

The sacral micturition center is under the influence (predominantly inhibitory) of the central nervous system. Normally the pressure in the bladder remains low (less than 20 cm of water) as the bladder fills, as depicted in Figure 2. Normal bladder capacity is between 350 and 550 ml, and the first urge to void is normally felt between 150 and 250 ml. The urge to void is inhibited by the central nervous system until voluntary micturition is initiated by cholinergically mediated stimulation of the detrusor muscle via the nervi erigentes. Normal micturition requires the coordinated relaxation of the bladder outlet and urethra.

Other structures important in micturition, such as the prostate in men and the pelvic floor musculature in women, are shown in Figure 1.

Disorders of micturition in the elderly can result from disruption of any of these components of normal micturition.

Causes of Incontinence

Table 1 lists the causes of urinary incontinence in the elderly. As is the case with much of the illness seen in the elderly, the causes are often multiple, and interact with each other in complex ways.

It is useful to distinguish between the causes of

*Elsewhere in this issue is the article "A Guide Through the Maze of Long-term Care," which bears on this subject.

TABLE 2.—*Types of Established Incontinence*

Types of Incontinence	*Manifestations*	*Common Causes*
Stress	Leakage of small amounts of urine with increases in intraabdominal pressure	Prolapse of pelvic structures in women Sphincter damage Uninhibited bladder contractions may be involved
Urge	Leakage of urine due to inability to delay voiding long enough to reach toilet after urge to void is perceived	Uninhibited bladder contractions—associated especially with central nervous system disease such as stroke, dementia, Parkinson's disease, multiple sclerosis, prostatic obstruction, postprostatectomy
Overflow	Leakage of small amounts of urine without urge to void or ability to void normal volumes	Anatomic obstruction (prostate, urethral stricture) Hypotonic bladder (diabetes, syphilis, spinal cord compression) Anticholinergic drugs
Total	Complete lack of control over voiding	Sphincter damage Nerve damage (peripheral or spinal cord injury) Dementia (severe)*

*Incontinence may initially be nocturnal or intermittent but often becomes constant as cognitive impairment worsens.

transient versus *established* incontinence because the pathophysiology, prognosis and implications for management are different in these two groups.

Transient Incontinence. Transient incontinence is most often associated with acute medical conditions, psychologic responses or iatrogenic factors; appropriate management can often prevent these episodes of incontinence from becoming an established problem.

Acute urinary tract infections frequently precipitate incontinence. It should be noted that the relationship of chronic bacteriuria and pyuria in older persons to incontinence is not clear.[13,14] Any elderly patient who is incontinent and has pyuria and bacteriuria should be treated for the infection; if the infection is irradicated and incontinence persists, then further evaluation is indicated (see below).

Any acute illness that is associated with fatigue, immobilization, confusion and hospital admission can precipitate incontinence. This is especially true of elderly persons who, upon becoming ill and entering a hospital, lose the adaptive mechanisms they have developed at home to cope with urinary frequency and urgency. Appropriate supportive management with attention to the environment, such as making toilet substitutes accessible, is crucial in preventing perpetuation of the incontinence. Many attitudes and behaviors of hospital staffs may contribute to the development and persistence of this type of transient incontinence.[11]

Drugs are another important iatrogenic factor that can contribute to incontinence. Because of the importance of the autonomic nervous system to normal micturition, drugs that affect this system can contribute to the development of incontinence. This is especially true of anticholinergic drugs, which can cause urinary retention and overflow incontinence. Sedatives and hypnotics, which diminish the recognition of cues for normal micturition, can also be a factor in the development of urinary incontinence.

Overflow incontinence caused by urinary retention is important to recognize because it is reversible, and can itself lead to complications such as hydronephrosis and postobstructive diuresis. In addition to drugs, fecal impaction and acute spinal cord compression are other reversible causes of this type of incontinence.

Psychological factors can be important in precipitating and perpetuating urinary incontinence. Incontinence can help fulfill the needs for dependency and secondary gain of those who are depressed. It is also a convenient way to express anger and hostility. Attention to these psychological factors is important in managing both transient and established incontinence.[11]

Established Incontinence. Table 2 defines different types of established incontinence that can be seen in the elderly.

The causes of established incontinence listed in Table 1 are relatively straightforward. Two of these deserve further mention because they are extremely common: *stress urinary incontinence* in women and the *uninhibited bladder* in both men and women.

Stress Urinary Incontinence. Leakage of urine during exercise, coughing, sneezing, laughing and the like can be extremely distressing for elderly women. This condition is most often caused by an anatomical abnormality—hypermobility of the proximal urethra that results in a position outside

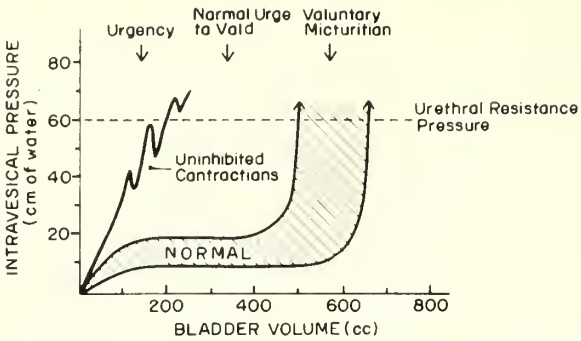

Figure 2.—Pressure-volume curves depicting the normal relationship and uninhibited bladder contractions.

TABLE 3.—*Basic Evaluation of Urinary Incontinence in the Elderly*

History	
Physical examination	
Analysis and culture of urine	
Postvoid residual determination	
Men	*Women*
Urine flowmetry	Voiding cystourethrogram
Cystoscopy	Cystoscopy
Cystometrics	Cystometrics
Other urologic studies as indicated*	

*Urethral pressure profile, sphincter electromyography (see text for details).

the intra-abdominal cavity. This allows intra-abdominal pressure to contribute to leakage of urine, rather than continence as it does when the proximal urethra is intra-abdominal.[15] Multiparous, postmenopausal women with weakened pelvic floor musculature are most susceptible to this condition.

Many women with stress incontinence have uninhibited bladder contractions[15] (see below), but the relation of these contractions to the causes and management of this condition is unclear.[15,16]

Uninhibited Bladder. The terms uninhibited neurogenic bladder, detrusor hyperreflexia and unstable bladder have all been used to describe urinary symptoms associated with uninhibited bladder contractions. These contractions often occur at low bladder volumes—and when bladder pressure exceeds urethral resistance, leakage of urine can occur (see Figure 2).

Between 50 percent and 75 percent of elderly incontinent persons will have uninhibited contractions on cystometric testing.[17-19] They also occur in 20 percent or more of women with stress incontinence,[15] and in up to 50 percent of men with postprostatectomy incontinence.[20,21]

It is important to recognize that this urodynamic finding may result from a wide range of genitourinary, as well as neurological, disorders.[22] In addition, the specificity of these uninhibited contractions for urologic or neurologic pathological conditions in the elderly has not been established because the prevalence of this finding in healthy continent elderly persons is not known.[18,23]

Uninhibited bladder contractions are often held responsible for the common complaints of urinary frequency and urgency in the elderly. When combined with locomotor disturbances, these contractions certainly could be responsible for the urge incontinence so common in this population. It is on this basis that anticholinergic drugs, which inhibit bladder contractions, are used to treat urge incontinence (see below).

Diagnostic Approach

In his "Treatise on the Decline of Life" (1853) Van Oven said of urinary incontinence in the elderly, "This is a most miserable Condition, and after it has been long existing, is often irremediable."

Over a century later the attitude that urinary incontinence is part of the decline in life, and that it is often incurable, too frequently becomes a self-fulfilling prophecy.

The first and most important step in approaching urinary incontinence in the elderly is to recognize it as a problem worthy of thorough diagnostic evaluation. A basic scheme for evaluating the disorder is shown in Table 3. The importance of searching for reversible causes of transient incontinence (shown in Table 1) throughout the evaluation should be emphasized.

History

A detailed history, obtained from either the patient or someone who knows the patient well, is important in defining the nature and extent of the problem. Although no particular set of symptoms is specific for any type of incontinence, a history of surgical operation, urinary infection or drug ingestion, as well as urgency, dysuria, hematuria, hesitation, sensation of bladder fullness, and the frequency, timing and volume of incontinence, can all be important diagnostic information.

Physical Examination

In addition to a careful examination of the genitourinary system, palpation of the abdomen

for a distended bladder is important in diagnosing urinary retention with overflow incontinence. If a distended bladder is found, examination for fecal impaction and neurologic examination to look for signs of spinal cord compression should be done.

Neurologic examination, in addition to identifying signs of cord compression, can be helpful in identifying other pathological conditions that can contribute to incontinence. This would include examinations of rectal sphincter tone, perianal sensation and the bulbocavernosous reflex, as well as sensation and reflexes in the lower extremities.[22]

Analysis and Culture of Urine

Because incontinence is often precipitated by urinary infection, routine analysis and culture of urine specimens are important initial studies. Although bacteriuria and pyuria are common in the elderly and often asymptomatic,[13,14] in the presence of the recent onset of urinary incontinence, an attempt should be made to eradicate any documented infection.

Postvoid Residual Determination

This is a simple yet often overlooked diagnostic test. In addition to yielding important information in itself, the urine obtained can serve as a clean specimen for culture. Residual urine of more than 20 to 30 ml obtained within a few minutes of voiding is abnormal and should prompt an evaluation for conditions such as outflow obstruction or a hypotonic bladder.

Radiological Studies

One of the most frequently ordered tests in evaluating incontinence is an intravenous pyelogram (IVP). Given the small but definite risk of this test (especially in the presence of diseases common in the elderly such as diabetes, chronic renal failure and heart failure)[21] and the fact that the same information can be obtained from more sensitive and specific procedures, it is unclear why IVP's are so frequently ordered.

If visualization of the dynamics of micturition is desired, a voiding cystourethrogram, with stress maneuvers when appropriate, should be done. Ultrasonography is safer and just as sensitive as an IVP in excluding hydronephrosis, and cystoscopy is more sensitive and specific than radiographic studies in defining urethral and bladder pathological conditions.

TABLE 4.—*Therapeutic Modalities for Urinary Incontinence in the Elderly*

Supportive measures
Appropriate attitudes
Accessible toilet substitutes
Bedside commodes
Urinals
Absorbent bed pads
Protective undergarments
Toileting routines ("bladder retraining")
Avoidance of iatrogenic complications
Excessive sedation
Inaccessible toilets
Drugs adversely affecting bladder or urethral function
Drugs (See Table 5)
Surgical procedures
For pelvic prolapse in women
For bladder outlet obstruction in men
Mechanical and electrical devices
Artificial sphincters
Electrical stimulators of sphincter musculature
Catheters
External (condom or "Texas")
Suprapubic
Indwelling

Urologic Studies

Many types of urologic studies are available to evaluate incontinence, including cystoscopy, cystometrics, urine flow studies, measurements of urethral pressure (urethral profilometry) and recording of the electrical activity in sphincter muscles (sphincter electromyography).[25-28] An apparatus designed to simultaneously display voiding cystourethrography and pressure-flow studies has been used in Great Britain to evaluate incontinence.[28]

The most sensitive and specific urologic procedure for evaluation of incontinence is direct visualization of the urethra and bladder by cystoscopy. Because urinary incontinence, as well as abnormalities on any one of the urodynamic tests, can reflect a variety of underlying disorders, elderly persons in whom there is no well-defined cause of transient incontinence (or whose incontinence has not cleared despite treatment for one of these causes) should have cystoscopy.

The usefulness of urodynamic tests in the evaluation of urinary incontinence in the elderly is controversial.[29] As mentioned above, the specificity of these tests is unknown in these patients, and they are invasive, expensive and often technically difficult to perform and interpret in this population. In addition, some studies of drug therapy for incontinence could not find a clear correlation between symptomatic improvement and changes

in some urodynamic tests.[20-33] Some investigators feel these tests are crucial for diagnosis and therapy,[10,19,31] whereas others feel the tests are not needed for many patients who can be diagnosed using an algorithm that is based on history and physical examination findings.[35,36]

Despite this controversy, urodynamic tests can realize that symptoms do not accurately predict be useful in some patients. It is important to urodynamic abnormalities; this was nicely documented in a study of 15 elderly men with "typical symptoms of prostatic obstruction."[29] Half of these men had uninhibited bladder contractions alone, without obstruction shown on urodynamic testing. Urine flowmetry can be a valuable screening test for men with symptoms of outflow obstruction; flow rates of less than 10 ml per second are abnormal, and rates greater than 25 ml per second usually rule out obstruction.[25] Cystometrics and other pressure-flow studies can identify uninhibited bladder contractions or sphincter weakness. In the absence of other correctable pathological conditions, abnormalities detected on these types of studies can be used to guide trials of drug therapy for the incontinence[37] (see below and Table 5).

Management

Table 4 lists several therapeutic modalities available to treat urinary incontinence. It is unfortunate, yet important to recognize, that none of these has been well-studied in carefully characterized groups of elderly incontinent subjects. This should not, however, imply that these forms of treatment are without value for some elderly incontinent patients.

Supportive Measures

Various types of supportive measures may be especially valuable in managing incontinence in the elderly that is associated with acute illness. Appropriate attitudes and environmental manipulations, such as making toilet substitutes readily available, can be very important.[11,38] Bladder retraining, mostly in the form of specific toileting routines and symptom monitoring has been advocated for certain patients,[39-41] but remains of uncertain value in the elderly. Special absorbent bed pads and undergarments may prove very effective not only in managing the incontinence, but in preventing skin irritation and excessive costs of nursing time and laundry.[11,42,43]

Drugs

Several different types of drugs have been used to manage incontinence (Table 5). Although many studies of these drugs have included small numbers of elderly patients,[30,33,44-49] they have important methodologic problems. Despite the difficulties with these studies, it does appear that some drugs will affect the symptoms and, in some instances, the urodynamic abnormalities of elderly incontinent persons.[30,33,45,49]

Until further studies are done it is reasonable to treat those patients who have established incontinence and uninhibited bladder contractions with an anticholinergic drug—such as oxybutinin (5 mg three times a day), imipramine (25 to 50 mg three times a day) or propantheline (15 to 30 mg three times a day). These drugs may cause bothersome side effects, such as dry mouth and visual difficulty, as well as urinary retention, and must be used carefully. When sphincter weakness is present alone or along uninhibited contractions, a trial of small doses of an α-adrenergic agonist (such as pseudoephedrine, 15 to 30 mg three times a day) might be of value. These drugs must be used carefully in the presence of systemic hypertension and organic heart disease.

Topically administered estrogens have been used to treat urinary symptoms related to atrophic vaginitis. Although they are of theoretic value in the management of stress incontinence, data on their efficacy for this condition are not available. Topical intravaginal estrogens are rapidly absorbed to pharmacologic blood levels; potential complications, as have been described for systemic estrogen therapy for other conditions in the elderly, should therefore be kept in mind[50] (Table 5).

Surgical Procedures

Several different types of surgical procedures can ameliorate or even cure incontinence that is related to prolapse of pelvic structures in elderly women. These procedures should be considered for those who can tolerate this type of operation.

An operation is clearly indicated for overflow incontinence in men when it is related to anatomical obstruction. The surgical mortality for this type of procedure is extremely low, even in the elderly[51]; avoiding a surgical procedure on the basis of age alone, and treating the condition with catheters (which may have a higher morbidity)

does not seem justified. Negative effects of this type of operation, such as the potential for impotence, should be considered when making a decision.

Electrical and Mechanical Devices

Various types of artificial sphincters and electrical stimulators of sphincter muscles have been tried in the management of incontinence.[11,52] Many require a surgical procedure; others are too difficult for most elderly to manipulate. Until these techniques are further refined, they have limited application in these patients.

Catheters

Although catheters may be required for the management of urinary incontinence in many old persons, these devices are probably used far too frequently—and often as a matter of convenience.

External catheters for men may substantially reduce the risk from indwelling catheters, but are far from problem-free. Local skin irritation and severe balanitis are common complications. Accordingly, their use should be avoided when other types of therapy, such as drugs or toileting routines, might solve the problem.

Indwelling catheters are the major source of

TABLE 5.—*Drugs Used to Treat Urinary Incontinence*

Drugs	*Dosages*	*Mechanisms of Action*	*Types of Incontinence*	*Potential Side Effects*
Anticholinergic				
Propantheline	15-30 mg three times a day		Urge incontinence with uninhibited bladder contractions	Dry mouth Blurry vision
Imipramine	25-50 mg three times a day	Diminish uninhibited bladder contractions		Elevated intraocular pressure
Oxybutinin	5 mg three times a day		Stress incontinence with uninhibited bladder contractions	Constipation
Dicyclomine	10-20 mg three times a day	Increase bladder capacity		Postural hypotension, cardiac conduction disturbances (imipramine only)
Flavoxate	.....			
Emepronium*	.....			
α-Adrenergic agonists		Urethral sphincter contraction	Stress incontinence with sphincter weakness	Headache Tachycardia Elevation of blood pressure
Pseudoephedrine	15-30 mg three times a day			
Phenylpropanolamine	50 mg twice a day			
Imipramine	25-50 mg three times a day			Imipramine—see above
Cholinergic agonists				
Bethanechol	10-30 mg three to four times a day	Bladder contraction	Overflow incontinence with atonic bladder	Bradycardia, hypotension, bronchoconstriction, gastric acid secretion
α-Adrenergic antagonists		Urethral sphincter relaxation	Overflow incontinence with hyperactive urethral sphincter	Postural hypotension, nasal stuffiness, pupillary constriction
Phenoxybenzyline	20-200 mg four times a day			
Estrogens				
Systemic		Increase periurethral blood flow, muscle strength and sphincter tone	Stress incontinence (women)	Endometrial cancer, elevated blood pressure, gallstones, cardiovascular (stroke, embolus, myocardial infarction)
Estrone	0.3-0.625 mg every day			
Estradiol	1-2 mg four times a day			
Topical				
Estrone	1 gram twice per week			
Investigational				
Prostaglandin inhibitors		Inhibit bladder contractions	Incontinence with uninhibited bladder contractions	Gastric irritation
Indomethacin	25-100 mg twice a day			
Flubiprofen	50 mg three times a day			
Calcium antagonists				Hypotension, reflex tachycardia, drowsiness (nifepidine)
Nifepidine	10-20 mg twice a day			
Baclofen	5-10 mg twice a day			Weakness, insommia, pruritis (baclofen)

*Not available in the United States; used in Europe.

nosocomial urinary tract infections, which account for 35 percent of all nosocomial infections, and occur in about 2 percent of hospital admissions.[53,54] Many of these infections remain asymptomatic, but their presence predisposes to symptomatic infection, as well as sepsis and death. Certain factors, such as advanced age, female sex and serious underlying illness, predispose persons with catheters to the development of bacteriuria.[55] Although antimicrobial therapy may delay the development of bacteriuria,[55] antibiotic prophylaxis (using irrigation solutions) is not effective in preventing catheter-associated infections.[54,56] Despite evidence that bacteria migrate from the urethral meatus to cause catheter-induced infection,[57] vigorous daily meatal care appears to increase, rather than decrease, the risk of catheter-induced bacteriuria.[58] Routine catheter irrigation and frequent meatal cleansing are also expensive and time-consuming. Unless further research proves them valuable, these techniques should be avoided.

It is clear that indwelling catheters should be used only when no other form of therapy is practical—that is, in elderly patients with intractable incontinence and skin breakdown that can be exacerbated by contact with urine, in those with outflow obstruction that cannot be corrected surgically or in cases of persistent residual urine that predisposes to recurrent symptomatic infections or renal impairment. When indwelling catheters are used, meticulous attention to sterile closed drainage and adherence to other basic guidelines are important in reducing morbidity from these devices.[54,59]

Directions for Research

Urinary incontinence is one of the many areas of geriatric medicine that is ripe for well-designed clinical research. Several lines of investigation are suggested by the above discussion:

- The development of descriptive data that characterize those elderly who are incontinent. Determination of factors that will help divide this group into subgroups that will have relevance to further research on the causes, prevention, prognosis and management of the condition should be emphasized.
- The development of more refined techniques for the diagnostic evaluation of incontinence in the elderly, with emphasis on the sensitivity and specificity of urodynamic tests, as well as their value in the management of the condition.
- The development of new and better management techniques. This should include rigorously controlled studies of treatments such as drugs and bladder training routines, as well as the design of new and better technology for managing elderly persons with intractable incontinence. The latter would include improving currently used diapers, and external and indwelling catheters.

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Geriatric Education in a Teaching Hospital: The Role of Geriatric Services

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Geriatric education and training are most successful when taught in a setting that provides the medical and social services that elderly persons often require. At Mount Zion Hospital and Medical Center, medical students and trainees participate in several geriatric services that introduce them to the special health needs of the elderly, including the ambulant and the homebound. In the Mount Zion/University of California, San Francisco, geriatric education and training program, we have defined three principles of geriatric medicine that are unique to the field and are best applied directly within the service setting. This setting emphasizes (1) the special body of knowledge regarding aging and health care of the elderly, (2) the importance of assessing functional capacity and (3) the role of the health team. Our experience indicates that when students and trainees observe the application of these principles in a range of geriatric services they begin to understand the complex health problems with which geriatric medicine is concerned.

In the highly regarded Institute of Medicine report *Aging and Medical Education*,[1] it is stressed that geriatric medicine is best taught in a setting that involves ongoing health services to the elderly. The point is made that the traditional university hospital that treats older persons who are acutely ill is not the place for medical students and graduate trainees to learn about the long-term medical care of aging patients. Indeed, geriatric medicine is unique in its concern with the management of chronic illness and in its reliance on a variety of geriatric services designed to encourage optimal functioning and independence in the face of debilitating disease.

Calvert and Koch[2] and others have also emphasized the need to teach geriatric medicine in a variety of health care and service settings so that a "balanced view of the elderly" and the management of long-term illness can be conveyed. Williams and co-workers[3] reported that before the geriatric medicine education program could be inaugurated at the University of Rochester, School

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of Medicine, a "full range of services and levels of care for the chronically ill and aged" had to be developed.

Mount Zion Hospital and Medical Center, a major affiliate of the School of Medicine at the University of California, San Francisco (UCSF), has based its geriatric medicine education program on a broad spectrum of geriatric services.[1] For many years, Mount Zion Hospital has provided various geriatric services in response to the need for improved health care among the San Francisco elderly community. The geriatric medicine education and training program evolved only after many of these services were available. In this paper we discuss the underlying principles of our geriatric medicine education and training program, describe some of our geriatric services and explain how they enhance the application of these principles. (We will not cover those specific educational and training objectives that are met by seminars, lectures, long-term care experience and research activities.)

Principles of Geriatric Medicine

Brocklehurst and Hanley,[4] Besdine[5] and others have offered descriptions and definitions of the unique characteristics of geriatric medicine. We have developed three principles that express the special qualities of geriatric medicine and which best can be demonstrated in a geriatric service setting. (1) Geriatric medicine encompasses a special body of knowledge of the aging process and health care of the elderly that includes physiological and psychosocial changes with which physicians must be familiar. (2) The assessment of functional capacity, in addition to precise diagnosis, is essential to the long-term management of elderly patients. (3) Geriatric medicine requires the participation of a health team that can use the appropriate health and social service agencies to augment medical care. We believe the success of a geriatric medicine training and education program requires an atmosphere that emphasizes a positive, caring attitude toward improving the health and well-being of aging patients and that stresses the dignity and importance of the individual patient.

The Geriatric Education and Training Program

The Mount Zion Hospital/University of California, San Francisco, geriatric education and training program provides training at the undergraduate, graduate and postgraduate levels. (UCSF is also developing a training and education program, under the aegis of Carol Winograd, MD, at San Francisco General Hospital, a major teaching facility of the University.) Undergraduate, third-year and fourth-year medical students have the opportunity to elect a one-month geriatric clerkship that offers a full range of geriatric clinical and service experiences at Mount Zion Hospital. In addition, those fourth-year students who come to Mount Zion Hospital for the required Family and Community Medicine course, work in the geriatric medical clinic and medical screening clinic and are exposed to selected geriatric services. Third-year students who do their required core-curriculum medicine clerkship at Mount Zion Hospital often are involved in geriatric consultations of their patients and in some geriatric teaching conferences.

Postgraduate or fellowship training in geriatric medicine has been offered by Mount Zion Hospital's Department of Medicine since 1978. (Mount Zion Hospital is indebted to the Henry J. Kaiser Family Foundation for the initial three-year grant that funded its first geriatric medicine fellowship.) The program was expanded in 1979 as a result of an Administration on Aging award to Mount Zion Hospital and Medical Center and the University of California, San Francisco, School of Medicine. The geriatric fellows, who have completed their internal medicine residencies, spend one to three years in training and research in geriatric medicine at Mount Zion Hospital and the University of California. In their roles as geriatric fellows, they serve as clinical preceptors to the medical students and provide consultation services to the house staff. We believe that the presence of knowledgeable and enthusiastic physicians, pursuing a special interest in geriatric medicine, can have a positive influence on the attitudes of the medical students and house staff about caring for aging patients.

The Role of Geriatric Services

The geriatric services at Mount Zion Hospital range from acute inpatient care to posthospital ambulant and home care as well as long-term care for both the institutionalized and independent elderly. In all of the services, emphasis is placed on knowledge of the aging process and special health needs of this population, assessment of

functional capacity and team approach to health care.

The Geriatric Outpatient Clinic

This clinic meets two half days each week and is conducted by the geriatric faculty, the geriatric fellows, medical students and geriatric nurse practitioner trainees. Geriatric social workers are present and senior psychiatric residents are on call.

All of the patients seen in the geriatric clinic are 65 years of age or older and most are the "old-old," that is, 75 years or more. They may be seen for consultation only or for ongoing care. The patients most frequently seen are those with multiple problems or with behavioral problems, including memory loss and confusion. A substantial number of the latter have iatrogenic or drug-related problems, depression or previously undiagnosed metabolic or endocrine problems.

The Geriatric Evaluation Service

The Geriatric Evaluation Service was developed recently to give consultation on patients referred by private physicians, long-term care facilities or families. Assessment of these patients often results in a diagnosis of a "reversible dementia." This service has been a gratifying experience for the fellows and students because by applying their knowledge of geriatric medicine they have the opportunity to observe improvement in cases previously labeled as hopeless.

The geriatric staff also provides inpatient consultations to the house staff and attending physicians, and often significant but treatable problems, which have presented atypically, may be found. While geriatric consultation is not a requirement, it is becoming more common as the house staff becomes aware of its value.

The Geriatric Screening Clinic

The Geriatric Screening Clinic, staffed by a geriatric social worker, the fellows and medical students, offers a free health assessment that includes a physical examination, laboratory work, psychosocial evaluation, and dental and hearing tests to persons 60 years and older who have no continuing source of health care and who have not had a health examination for at least a year. When appropriate, follow-up care is arranged or referral is made to one of the Mount Zion Hospital geriatric services. The goal of the screening clinic is to identify and treat disease or health-related problems of elderly people who either avoid or have no access to health care.

The geriatric clinic, screening clinic, geriatric evaluation service, and inpatient consultation service are excellent settings in which to apply the three principles of geriatric medicine. For example, atypical presentations of disease and drug reactions emphasize the need to be knowledgeable about pathophysiological and pharmocological changes with age. The problems that arise as a result of economic instability or psychosocial losses in old age require not only a special sensitivity on the part of physicians but also the knowledge to call on the appropriate health team members. The social worker, nurse, physical and occupational therapist, psychologist, and dentist often play an important role in the management of a clinic patient. Finally, the clinic setting provides the opportunity to stress the importance of the patient's functional capacity in addition to the underlying diagnosis. Long-term management of chronic disease invariably requires the assessment of functional capacity because it can vary substantially among patients with the same diagnosis. Coping ability and functional capacity may have a far greater impact on a patient's course than the diagnosis of disease itself. These clinical settings dramatize this important feature of geriatric medicine.

Home Care

Home Care, the oldest of the hospital geriatric services, was started more than 30 years ago in recognition of the special medical problems of elderly patients. It provides quality care for the homebound, the discharged hospital patients, and those who would have to be admitted to institutions if Home Care services were unavailable. Home Care offers medical care, nursing, physical, occupational and speech therapies, social service and home health aides. Major emphasis is placed on rehabilitation, counseling, nursing care and ambulation training for those who can progress outside of the home. For many patients who are becoming independent, there is a direct link between Home Care and the other Mount Zion Hospital geriatric services.

Medical house staff are assigned to Home Care on a two-month rotation and medical students can elect to participate in home visits. The geriatric fellows often provide consultation to Home Care case conferences.

In two companion articles, Hoffman[6] and Bis-

sonette[7] discuss the teaching potential of the Home Care setting and list a series of educational objectives in their Home Care programs. Of special importance are (1) the principles of geriatric medicine, including intervention and prevention; (2) an awareness of environment and social factors as influences on health, and (3) the health team approach to health care. We also wish to stress that it is in the home environment that functional capacity best can be observed. Here the health worker and, in particular, the physician, are forced to consider not only the disease, but the patient's home circumstances, which may or may not be advantageous to the ongoing care program. It has been our experience that students and trainees who spend time on the Home Care service or the other services that go into the home, are more likely to develop an understanding of and appreciation for elderly patients and the special qualities of geriatric medicine.

The Ruth Ann Rosenberg Adult Day Health Care Program

This program, begun in 1975, is a medically oriented daytime service that was modeled after the British day hospital. The objective of the program is to provide the kinds of health support services that allow the elderly with serious medical problems to remain in their homes and to be as independent as possible. The services available are transportation, nursing care, social service, physical, occupational and speech therapies, therapeutic recreation, socialization and noontime meals. Often, patients come to this service after having "graduated" from Home Care or having been discharged from hospital.

The geriatric fellows provide medical consultation to the adult day health team and serve as the primary-care physicians to those patients who are referred from the clinic. The medical students are assigned to interview selected patients to learn about both their medical histories and their personal lives. In this way, we are trying to expose the students to the person rather than to the disease. This exercise often has altered some of the students' negative attitudes as well as helped them to develop good interviewing skills with older people.

The Adult Day Health Care Program, with its stress on medical and psychosocial care, is an ideal setting for students and trainees to observe the role of the team in health-care delivery and maintenance. As it evaluates the needs of an individual patient, the team must consider not only the list of diagnoses, but also psychological and physical functional capacity, financial status, and mobility inside and outside the home. The team approach brings together the special knowledge of many disciplines, which is essential for optimal care.

A day health care program that offers health and support services to the frail elderly, who otherwise might need institutional care, is an excellent means of demonstrating an important alternative in long-term care. The day health care approach is concrete evidence that with appropriate services, elderly persons can maintain independence and dignity in spite of debilitating disease. Certainly, it is an alternative that is likely to influence the development of future health care systems.

Project OPEN and the Multipurpose Senior Service Program (MSSP)

These are two research and demonstration programs designed to evaluate the effectiveness and cost of the provision of medical and social services based on a coordinated case-management system. It is hoped that these projects will show that this model is cost-efficient as well as helpful to the frail elderly in maintaining independence and quality of life. These projects provide services that ordinarily are not covered by Medicare or Medicaid.

The case-management concept includes a home visit by a case manager, team assessment and coordination of all needed services, including respite care and escort services. A citywide consortium of agencies, including Mount Zion Hospital's Geriatric Services, brings together all necessary services. The data from these projects will show whether it is more costly or less to provide health and social services on an "as needed" basis, as is done at present, or on the proposed case-management basis.

The geriatric fellows often participate in conferences and have the opportunity to observe the team approach to case management. Moreover, they are available to the staff for consultation and frequently refer clinic patients to Project OPEN and MSSP. The medical students are assigned to a case manager to make home visits and to observe the assessment process by a nonphysician. In addition, the experience with these projects

gives students and trainees exposure to health policy issues and health services research.

Geriatric Information, Counseling and Referral Program

This program provides crisis intervention and appropriate referrals so that elderly persons receive the right service at the right time. It also offers assistance with social, emotional, financial, legal, personal and convalescent problems. House calls are usually made by the social worker to evaluate the patient's home situation, referrals are made to appropriate services and agencies and follow-up is continued as long as is necessary.

The program also demonstrates to students and trainees the importance of the health team in handling the complex problems of the elderly. A medical crisis often is confounded by financial, social or emotional concerns. Frequently, it is the social worker or the nurse who, being more aware of community resources, may "bail out" a patient involved in such a medical-social crisis. When students and trainees learn to use the expertise of others, they have learned the importance of the health team contribution.

Mount Zion Hospital sponsors several other geriatric services that are not discussed in detail in this paper. The In-Home Arts Program brings artists and writers to elderly patients who are restricted to their homes because of chronic illness or severe depression. Often, this service is used by the Home Care staff to enhance the lives of these homebound patients. The Social Day Care Program assists elderly persons to make the transition from an isolated or a protected setting to senior centers and other community programs. Mount Zion Hospital also offers nutrition and medical education in an Outreach Program to senior groups, and to staff and volunteers in community senior centers and agencies. The geriatric fellows and Geriatric Services staff all participate in this activity. While these programs are not central to the geriatric education and training program, our students and trainees are aware of them and learn that they contribute to the well-being of the elderly community.

Conclusion

We have presented three principles of geriatric medicine that we believe are most effectively demonstrated in a training and education program that incorporates a variety of geriatric services. The special qualities of geriatric medicine, as articulated in these principles, can be learned best in a setting where the multiple health needs of the elderly are met. When students and trainees are exposed to the practice of geriatric medicine in the clinic, the day health care center, the home and the community agencies, they begin to understand the complex health needs of older persons and what can be done to meet these needs. We concur with T. Franklin Williams' statement:

> The chief lesson I have learned is the necessity for tying the teaching program into an environment where care is needed: an environment which cuts across as many of the various levels of care needed by elderly people as possible. If we can achieve this, in various programs, we have a good chance of success with the teaching programs. Otherwise, they will probably fail.[8]

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Specialized Geriatric Assessment Units and Their Clinical Implications

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Geriatric assessment units are among the several innovative responses by members of the US health care system to the many unmet needs facing elderly people who are frail and ill. Based on British models, these units are designed to improve the assessment of medical and psychosocial problems, to provide therapy and rehabilitation, and to determine optimal posttherapy placement at as high a level of independent functioning as possible. While generally similar, the structures and functions of various North American units vary considerably in such areas as type of patients accepted, amount of rehabilitation carried out and type of institutional setting (such as chronic-care hospital, acute-care hospital or outpatient facility). These differences have a bearing on outcomes. Though few experimental studies exist, impacts from the units appear to be substantial, and include more thorough diagnosis, higher levels of patient functioning and improved placement. Physicians can apply several of the lessons from these units to improve their care of elderly patients.

IT IS WELL KNOWN that elderly patients have more varied problems and health care needs than do most younger patients. These patients, particularly the frail elderly, characteristically have a multiplicity and chronicity of medical disorders, coexisting and interrelated psychological problems and progressive social isolation. Such numerous and interacting problems make caring for elderly patients particularly challenging.

There is a growing awareness that today's health professionals are failing to meet the complex care needs of the elderly. Among several fundamental deficiencies are inappropriately admitting patients to institutions who could better be living at home, lack of alternative care options or home-based services as substitutes for institutionalization, frequently incomplete and inaccurate medical assessments, lack of quality assurance mechanisms within nursing homes and other long-term care facilities, large inequalities among patients in medical insurance coverage and availability of community resources and a major shortage of well-trained and concerned professionals in primary and long-term geriatric care.[1-3]

Probably the most important of these problems is inappropriate admission to an institution. Many recent studies have concluded that a substantial proportion, perhaps a third, of elderly patients in long-term care facilities could live at home or in facilities providing lower levels of medical care.[4-8] Inappropriately admitting a patient to an

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institution is not only expensive financially but it incurs major social costs because dependency is created and the potential for patients to reenter society is lessened.[3,9-12]

Awareness of these dilemmas facing elderly patients has triggered several responses from the health care sector in the areas of education, research and clinical programs. Progress has been made with the establishment and growth of schools of gerontology, the organization of geriatric medicine curricula within medical schools and other schools of health professionals and the initiation of geriatric medicine fellowship programs. One major advance in clinical programs has been the establishment of specialized geriatric assessment and rehabilitation units. These latter specialized geriatric units have taken several forms. They have been established on acute-care hospital wards, in outpatient facilities and in long-term care institutions. Some units provide comprehensive diagnostic assessment without providing therapy, others provide only minimal assessment but extensive rehabilitation, and still others combine extensive assessment with therapy and rehabilitation. While distinct from one another, and clearly still experimental, these units seem useful in beginning to bridge the serious gap that exists in care services for the elderly.

In this paper, we describe these new and proliferating geriatric units and review their history and structures. The evidence that these units are providing new and important health services to elderly people is analyzed and implications for present practitioners in their approaches to elderly patients are discussed.

History

Geriatric assessment units originated in Great Britain between the World Wars. Dr. Marjorie Warren, generally considered the founder of modern geriatrics, initiated the idea of specialized geriatric assessment units during the late 1930's while in charge of a large London workhouse infirmary. The infirmary was filled primarily with bedfast and neglected elderly patients who never received proper medical diagnosis or rehabilitation. The high-quality nursing care kept the patients alive, while the lack of diagnostic assessment and active rehabilitation kept them disabled. She systematically evaluated these patients and began policies of mobilization and selective rehabilitation. She was able to get most of the long-bedfast patients out of bed and walking and, in some cases, could get them discharged. But even under her care, many patients could not fully recover, due to their previous prolonged immobilization. As a result of her experiences, Dr. Warren advocated comprehensive assessment and an attempt at rehabilitating all elderly patients before admitting them to long-term care hospitals.

The present British system for geriatrics, largely based on the work and reports of Dr. Warren, has served as a model for geriatric care in several countries with socialized or regionalized medical systems. Under this system, termed "progressive care," all elderly patients requiring admission to hospital, except those requiring intensive medical care, are admitted to an acute-care geriatric assessment unit. There, each patient receives a comprehensive assessment of medical, functional and psychosocial problems. Care plans are established on the assessment unit, usually by an interdisciplinary team, and the next level of care and placement is decided on—whether discharge to home, to a rehabilitation ward or to a long-term care facility. Length of patient stay on an acute-care assessment unit is two to three weeks. About half of the patients are discharged home, about a third are transferred to a rehabilitation or chronic-care ward and about a fifth die while on the unit. On the rehabilitation ward, the average length of stay is two to three months. About 60 percent of these patients are discharged home or to residential homes for old people, about 25 percent are transferred to chronic-care wards and about 15 percent die on the rehabilitation ward. On the chronic-care wards, the average length of stay is two to three years, and all but about 10 percent of patients remain there until death. Specific aspects of this progressive care model differ within Britain from one region to another. The age which constitutes the dividing line between internal medicine and geriatrics, for instance, may differ, or different regions may not agree on whether elderly patients with acute illness should be admitted to medical or geriatric wards. But two concepts are firmly held throughout Great Britain, regardless of regional differences: that elderly patients need a special, more broadly based and interdisciplinary approach to their care than do younger patients, and that no patient should be admitted to a long-term care facility without a careful medical and psychosocial assessment and at least a trial of rehabilitation.[13]

Several other countries (including Sweden, Australia, Norway and Israel) have built, or are

building, geriatric care systems similar to the British system, each with centrally located geriatric assessment units. Most of this development has occurred in the past decade and few lasting models or lessons for the United States have emerged beyond those already pioneered in Britain.[13,14] In no country yet has a well-controlled study been carried out to evaluate the effectiveness of these units. However, there seems to be general agreement that they are effective. In fact, many British geriatricians would consider such a trial to be unethical, so convinced are they of the clear value of geriatric units.

The United States, without a national health care system, has not developed an organized, cohesive method for dealing with the health care needs of its elderly. Medicare pays most acute hospital care and outpatient physician costs for persons older than 65, and Medicaid covers costs of long-term medical care for the indigent. Yet there is no structured system for assessing care needs of the elderly or for systematically supplying health services to meet these needs. As a result, local and regional medical organizations and groups have been fairly free to undertake limited demonstration and experimental projects to deal with locally perceived needs. These local movements have a long history of support from private foundations and universities. Several of these local projects have provided models for implementation and study elsewhere. Among such projects are several geriatric assessment units, based on the British model, which have the express goals of decreasing morbidity, improving functioning and preventing unnecessary institutionalization of elderly patients. In the following section, we analyze the goals and structures of existing geriatric assessment units in North America described in the literature.

Objectives and Structures of Existing Geriatric Assessment Units

Geriatric assessment units in North America are considerably varied in structure and setting. The predominant model is the inpatient unit within an acute-care general hospital.[15-19] Geriatric assessment units have also been established within extended care and long-term care facilities,[20,21] as well as in outpatient settings.[4,22,23] Geriatric units within teaching hospitals have further variations in structure and theme with the addition of research and educational programs.[16,19,24]

Some inpatient geriatric units in acute-care hospitals focus on comprehensive assessment and short-term treatment of acutely ill patients without providing extensive rehabilitative therapy.[16,25] Other inpatient units provide less assessment but prolonged rehabilitation,[20,24] while others provide both comprehensive assessment and extensive rehabilitation.[17,19] Some units are basically chronic-care facilities but with the important addition of assessment and intensive rehabilitation.[9,21] Outpatient units generally provide assessment and placement services without rehabilitation.[4,23]

The target patient populations that the geriatric units serve can be differentiated in several ways: sex ratios, geographic distance from hospital, level of care needed and types of problems. For example, most patients in Veterans Administration (VA) units are men, while in non-VA units, women predominate. Geographically, patients in VA facilities come from designated regional catchment areas that are usually quite large. Non-VA facilities generally derive their patients from their respective communities, usually much smaller than the VA catchment areas.

The various geriatric units differ in the types of patients they accept. For example, some units accept patients referred primarily for nursing home placement, but without acute illness.[4,23,25] Other units accept patients primarily with psychiatric problems.[15,26,27] Other units accept patients with acute medical illness.[16,28] And still other units select their patients from acute medical and surgical wards following recovery from the acute phases of illness but requiring further evaluation and rehabilitation.[17,19]

The interdisciplinary team approach for geriatric assessment has become the predominant mode of practice in North American geriatric evaluation units. These interdisciplinary teams usually consist of physicians, physician assistants or nurse practitioners (or both), nursing staff, social workers, psychologists and representatives from ancillary services, such as occupational therapy, physical therapy, dietetics, audiology and dentistry. Each team member is responsible for patient assessments in his or her field of expertise. The entire team monitors progress in assessment and reevaluates therapeutic goals and plans during periodic team meetings.

Several of the geriatric units combine their therapeutic functions with education and research in geriatric medicine and gerontology, often through university affiliation and support.[16,19] Some units possess other special features, such as

geriatric day hospitals[9] and outpatient follow-up clinics.[9,19,21] One program offers a preadmission home visit assessment service.[21] Others provide inpatient geriatric consultation.[19,28]

Evidence of Impact of Existing Geriatric Assessment Units

Most of the reports from North American geriatric assessment units identified in this review strongly suggest that comprehensive geriatric assessment and rehabilitation lead to improved patient outcomes. However, only one report used a true experimental design.[17] Most of the other reports were only descriptive studies, or quasi-experimental studies with precare and postcare comparisons, inadequate to demonstrate the effectiveness of the intervention—although all of the authors gave their impressions as to the value and usefulness of their own respective units. This section considers the data and impressions from the various studies.

The most widely measured patient outcome in these studies was functional status. Improvement in functional status is obviously important, and most studies that examined this aspect showed substantial improvement during a patient's stay on a given unit.[17,19,25]

Several researchers studied the impact of geriatric units on placement location. For example, Williams studied the effects of an outpatient evaluation and placement program on patients who were referred specifically for nursing home placement. He found that only 38 percent of these patients actually needed placement in nursing homes or in chronic-care psychiatric hospitals, 39 percent needed only board and care or health-related facilities and 23 percent were able to remain home, usually with the help of community services.[4] Analysis by an independent team of experts showed that 84 percent of patients had been "appropriately" placed after the program began, compared with only 50 percent to 60 percent before the establishment of the program. At the Sepulveda Veterans Administration Medical Center, Rubenstein and co-workers showed improvement over placement locations expected by medical staff on the referring service in 48 percent of patients treated on their unit.[19] Schuman and associates showed an increase in the number of patients discharged home from their chronic-care hospital, following institution of a new geriatric service, from 29 percent to 40 percent.[9] Balaban, dealing with a relatively independent population, showed that fewer patients were discharged to institutions from the special unit than from the control group of patients treated on the other inpatient wards—14 percent versus 18 percent—but this difference was not statistically significant.[17]

Another major area of impact of geriatric assessment units is the improvement of diagnostic accuracy, usually indicated by diagnosis of new, treatable problems. One unit diagnosed an average of nearly four new treatable conditions for each patient assessed, despite the fact that each patient had just received an ostensibly complete evaluation on an acute medical or surgical ward.[19] Another unit, which stressed psychiatric along with medical assessment, found 184 new major psychiatric conditions in the 241 patients transferred from acute medical and surgical wards.[16] Most of these new diagnoses seemed to stem from an awareness of the need for thoroughness in evaluating elderly patients, instead of reflecting substandard quality of care in the referring services. Excessive use of drugs is a well-known problem facing the elderly.[29] One inpatient unit, which emphasized improvement in drug regimens, was able to show a 43 percent reduction in number of prescription drug doses taken by patients during their stays on the unit despite a concurrent increase in number of diagnoses identified.[19]

The published reports on geriatric assessment units support the contention that inadequate health care is being delivered to the elderly and that major improvements can be made. These units provide several distinct aspects of care not available to patients in usual settings. Among them are comprehensive assessment (combining psychological, social and medical assessment), care delivery by interdisciplinary teams, rehabilitation, optimal placement and long-term follow-up. The reports support the idea, first proposed in Britain, that these kinds of units can have beneficial effects on such patient outcomes as placement location, diagnostic accuracy, functional status and appropriateness of therapy.

It still remains to be proved, however, that such units do indeed produce these benefits. Many of the described improvements in patient outcomes may have occurred simply with time alone. The failure of the one controlled study[17] to show many significant benefits compared with a control group is disappointing, but it is not enough to discourage most workers in the field of geriatrics, who cite various problems with making generalizations based on that study. Additional

well-designed studies are eagerly awaited. If benefit overall can be proved, it will also be important to determine which patients benefit the most from these types of approaches, and to more appropriately select patients. The financial effects of these units also need to be examined carefully. Such units could be clearly cost-effective if able to offset expenses by reducing use of other services, such as nursing-home care, readmittance to hospital, and pharmaceutical treatment. But even if these units do lead to increased overall medical costs, they could still be shown to be cost-effective if other measurable benefits were sufficiently great.

Clinical Implications

Even without experimental data that prove their overall effectiveness, descriptive information from these units suggests several ways for physicians to improve the care for the elderly, especially the frail elderly who are being considered for long-term institutional care. These data can be grouped into three major areas: more thorough assessment, more effective interventions and more careful determination of placement.

The primary purpose of assessment is to diagnose all active and potential problems for which therapy exists, as well as to identify the factors that have a bearing on the type and location of long-term management. Assessment of elderly patients can be improved by simply applying a rigorous and thorough approach. More time, rather than less, should be spent assessing an elderly patient than a younger patient, in view of the greater number of problems and the increased difficulty in obtaining a history and carrying out a physical examination. In addition, attention to several rarely performed kinds of assessment can yield remarkable benefits. For example, a formal assessment of functional status can identify specific areas in which the patient is failing and lead to specific therapeutic, rehabilitative or social support measures that might otherwise be overlooked.[30] Formal mental status evaluation, with attention to identifying reversible forms of dementia and treatable psychiatric problems, can also provide high yields.[31] The major precipitating causes for admitting patients to institutions—mental deterioration, incontinence and recurrent falls—have many reversible causes and should be systematically worked up. Side effects or interactions from the many drugs taken by elderly patients frequently cause major deterioration and even institutionalization and should be carefully considered. Home visits can often provide clues to a patient's deterioration as well as indicate aspects of the home that can be modified to permit continued stay there (such as improved lighting, handrails, hospital bed, raised toilet seat or wheelchair). The physician should call on other health professionals (for example, visiting nurses, occupational and physical therapists, psychologists, dietitians and social workers) to perform assessments in their respective areas of expertise. Experience from assessment units and programs in North America and abroad has taught the indispensability of the team approach. Another lesson is that uncovering even a relatively small remediable problem can lead to remarkable improvements in functional status of an elderly person.

After careful assessment, therapy should begin, and in elderly patients, it frequently differs from that in younger patients. Choice of medication and dosage, for instance, are usually different, and occupational and physical therapy become especially important. Additionally, interventions by social workers and mental health professionals are often essential in maintaining an elderly person at home. As with assessment, the team approach is an important part of therapeutic intervention.

Finally, determining optimal placement for a frail elderly patient with deteriorating ability to function needs careful attention rather than a hurried decision. The objective is to match each person's needs with optimal placement and care. The decision regarding placement should be based on maximum attainable health and function, rather than merely health functioning at the time of referral. Knowledge of the different levels of institutional care available in the community (such as board and care, intermediate care, skilled nursing care and chronic-care hospital facilities) as well as community home-health services is also essential for the decision. Again, a team approach is best.

Experience from the specialized geriatric units in North America and abroad indicates that they provide three major services: assessment, intervention and optimal placement for the frail elderly. It seems clear that practicing physicians can also provide these services, in conjunction with other appropriate health professionals, as long as they have the interest in and knowledge for doing so.

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A Guide Through the Maze of Long-term Care

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Complicated requirements regarding eligibility and coverage as well as variations in the availability of programs confuse even the most diligent physicians trying to advise elderly patients about health care services. Nevertheless, awareness of such government and community resources is critical because physicians play an essential role in assisting the elderly to receive maximum health care benefits, particularly during long-term illness.

PHYSICIANS WHO CARE for elderly patients frequently need to call on a variety of community resources. Alas, the complicated eligibility requirements, the regulations about how much of what is covered, and the varying availability of services place even motivated physicians in a labyrinth, often without so much as a guidebook, let alone a guide. A major factor that limits effective use of resources is the need to determine a patient's eligibility for the services he or she requires. To the extent that these programs are increasingly supported by public funds, physicians face a confusing plethora of alpha/numeric acronyms. The purpose of this paper is to provide a guide through the maze of federal programs designed to serve the elderly. Along the way, we hope to point out areas of overlap and of underservice. Finally, we will review available data to offer clues about how to identify those most likely to be admitted to institutions.

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Major Federal Programs

There are essentially four major federal programs that provide important health-related benefits for old people. Each operates under a different mandate and each is targeted to a different (but potentially overlapping) constituency. Each provides a different package of services. All but one of the programs (Medicare) are run in collaboration with one or another unit of government. Thus, the consistency of program operations varies from state to state and, in some cases, from county to county.

Table 1 summarizes the major federal programs for elderly persons. The most familiar, Medicare, more formally known as Title XVIII of the Social Security Act, is organized as an insurance entitlement program for acute medical care. It comprises two related parts. Part A covers primarily hospital care and a small amount of posthospital care. Part B deals with supplemental medical insurance and includes a variety of services that augment the medical care of the elderly. Virtually all people in this country 65 years or older are enrolled in Medicare. For Part A there is no additional cost and for Part B there is a small monthly premium.

Medicare is essentially a program that covers

acute illness, with a major focus on hospital care. It is organized similarly to most health insurance programs. It provides hospital coverage under a "reasonable cost" reimbursement formula and a limited amount of nursing home care in skilled facilities. The latter is intended to be a continuation of hospital care but at a lower (that is, cheaper) level. Patients must have had a minimum of three days in hospital to be eligible for skilled nursing coverage under Medicare. They are expected to have a condition that can respond to long-term care. The program operates, as most

TABLE 1.—*Summary of Major Federal Programs for the Elderly*

Program	*Eligible Population*	*Services Covered*	*Deductibles and Copayments*
Medicare (Title XVIII of the Social Security Act)			
Part A: Hospital insurance	All persons eligible for Social Security and others with chronic disabilities such as end-stage renal disease plus voluntary enrollees 65+.	Per benefit period, "reasonable cost" for 90 days of hospital care plus 60 lifetime reservation days; 100 days of skilled nursing facility (SNF); home health visits (see text).	$204* deductible and copayments of $51/day for hosp. days 61-90; $102/day for lifetime reserve days; $22.50 for SNF days 21-100.
Part B: Supplemental medical insurance	All those covered under Part A who elect coverage. Participants pay a monthly premium of about $10.	80% of "reasonable cost" for: Physicians' services; supplies and services related to physician services; outpatient, physical and speech therapy; diagnostic tests and x-rays; surgical dressings; prosthetics; ambulance; home health visits.	$60* deductible and 20% copayment.
Medicaid (Title XIX of the Social Security Act)	Persons receiving Supplemental Security Income (SSI) (such as welfare) *or* receiving SSI and state supplement *or* meet lower eligibility standards used for medical assistance criteria in 1972 *or* eligible for SSI *or* were in institutions and eligible for Medicaid in 1973. Medically needy who do not qualify for SSI but have high medical expenses are eligible for Medicaid in some states; eligibility criteria vary from state to state.	*Mandatory services* for categorically needy: Inpatient hospital services; outpatient services; SNF; limited home health care; laboratory tests and x-rays; family planning; early and periodic screening, diagnosis, and treatment for children through age 20. *Optional services* vary from state to state: Dental care; therapies; drugs; intermediate care facilities; extended home health care; private duty nurse; eye glasses; prostheses; personal care services; medical transportation and home health care services. (States can limit the amount and duration of services.)	None, once patient spends down to eligibility level.
Title XX of the Society Security Act	All recipients of Aid to Families with Dependent Children (AFDC) and SSI. Optionally, those earning up to 115% of state median income and residents of specific geographic areas.	Day care; substitute care; protective services; family counseling; home-based services; employment, education and training; health-related services; information and referral; transportation; day services; family planning; legal services; home-delivered and congregate meals.	Fees are charged to those with incomes greater than 80% of state's median income.
Title III of the Older Americans Act	All persons 60 years and older. Low income minority and isolated older persons are special targets.	Homemaker; home-delivered meals; home health aides; transportation; legal services; counseling; information and referral plus 19 others. (Fifty percent of funds must go to those listed.)	Some payment may be requested.

*Medicare deductibles are scheduled to increase. Hospital deductible under Part A is projected to be $256 by January 1982. Medical deductible under Part B has been increased to $75.

insurance programs, with a combination of deductibles and copayments. The deductibles are determined on the basis of the average cost of a hospital day and the copayments to approximately a quarter of a hospital day's cost. A similar system with copayment is used for nursing home days. In both cases, the copayments begin sometime after the patient has been admitted to the institution. The patient is eligible for coverage on a per-benefit-period basis. There are also limitations of coverage with regard to expenditures per episode of illness. Part B operates with similar deductibles and copayments, but it also has the complication of paying less than reasonable cost (defined on the basis of group norms and previous billing history). It is important to appreciate that Medicare is the major source of hospital payment for older people. Although it does not cover any substantial proportion of nursing home costs, it is the mechanism under which many other services (including physicians' services) to nursing home patients are reimbursed.

Medicaid is a welfare program authorized under Title XIX of the Social Security Act. This program is jointly operated by federal and state governments. The federal government provides between 50 percent and 78 percent of the state's cost of underwriting health services to the poor. Federal guidelines set minimum standards, which the state can then, at its option, build on to increase benefits or eligibility. The principal targets of the program are those persons covered under categorical welfare programs (such as families with dependent children, the aged, blind, permanently disabled and medically needy). The categorically needy components of the aged, blind and disabled were combined under a federally sponsored program, Supplemental Security Income (SSI), in 1974. The elderly are thus identified as being either SSI recipients or medically needy. Medicaid is a program designed to serve people who lack their own financial resources. Thus, there are no deductibles or copayments. However, many critics of the program have pointed out that it imposes a burden of poverty as a condition of eligibility. A person is required to divest himself of his own resources (the so-called spend-down requirement) before becoming eligible for Medicaid assistance. The program consists of two groups of services: mandatory services and a larger set of optional services. The latter can be provided at the discretion of the state, which can set limits on the amount and duration of such care. In fact, even the mandatory services can be expanded or contracted at the option of a state government. The states also have the ability to set payment levels, which cannot exceed what is paid for private care.

In contrast to the two programs just described, the next two are primarily social service programs with some medical components. Under Title XX of the Social Security Act (known as the Social Service Amendments), federal funds are paid to state government agencies as block grants based on state populations. The states are paid 75 percent of social service program costs up to their respective Title XX ceilings (90 percent for family planning costs). The eligible population includes those people covered under categorical welfare programs and, at the state's option, other groups identified on the basis of income or special needs. A wide variety of services are available under the program. General mandates of the program can be summarized under five broad goals: (1) to help people become or remain economically self-supporting; (2) to help people become or remain self-sufficient; (3) to protect children and adults who cannot protect themselves from abuse, neglect and exploitation and to help families stay together; (4) to prevent and reduce inappropriate institutional care as much as possible by making home and community services available, and (5) to arrange for appropriate placement and services in an institution when this is in a person's best interest.

Title III of the Older Americans' Act mandates a series of services targeted at older people (here defined as those who are 60 years or older). This program is supported by federal grants to state and then to local agencies to plan and coordinate services to older persons comprehensively. There are no income criteria, although some payment can be requested for those with income exceeding a threshold set by the local agency.

Home Care

As can be seen from even the brief summary in Table 1, several forms of care appear to be common across the various programs, although the eligible populations may vary. Perhaps the most universally available in theory is home care. Certainly, all of the programs provide at least some home-care services. Because of the growing interest in the use of home care as a way of keeping people in the community, it may be worthwhile

to spend a little time looking at the several programs.

Table 2 points out some of the differences in home care coverage provided under Medicare, Medicaid and Title XX. Medicare has recently broadened its coverage of home health services by rescinding the requirement that the patient previously be admitted to hospital for at least three days and by placing no limit on the number of visits covered under the program. However, persons eligible for coverage under Medicare must still meet certain criteria. They must be homebound and be certified by a physician as requiring "intermittent" skilled care; recertification is required every 60 days. Services can be provided only by a certified home health care agency. The patient must be certified as requiring one of several "primary services" (such as skilled nursing, physical therapy or speech therapy) to receive the secondary services (such as social work, home health aide services and occupational therapy). (Occupational therapy was promoted to a primary service as of July 1981, but in October 1981 it reverted to a secondary service with the option to continue it after the primary services are discontinued.) Except for light housekeeping around the patient's bed, homemaking is precluded.

Medicaid is more flexible in its eligibility requirements and in the services included. Although the need must be certified by a physician, the patient need not require skilled care (some patients may need lesser care). The state has the option of using the same homebound criterion as with Medicare. As noted earlier, a limited amount of home health care is mandatory under the federal guidelines, but states can opt for expanded home-care coverage, including personal home care. The latter represents health-related support services prescribed by a physician and given under the supervision of a nurse; these can encompass a wide variety of homemaking and other services.

The eligibility criteria for Title XX vary from state to state, as do the variety of services that can be provided under this program. Because Title XX has tripartite sponsorship, the variation can occur even within states at local options. One of the interesting aspects of the Title XX home-care program is the provision for three types of payment. Local agencies can opt to provide services directly themselves; they can contract with private agencies, or the recipient can enter into an agreement with an independent provider who does not work for any agency. The last provision has prompted much controversy in home-care circles about the problems of maintaining quality in the absence of any form of supervisory systems or institutional responsibility.

As can be seen in Table 2, home care represents a very small proportion of the total dollars in either the Medicare or Medicaid program. Medicare spent about 2 percent of its total program dollars on home health care; with Medicaid the

TABLE 2.—*Home Care Provided Under Various Federal Programs*

	Medicare	*Medicaid*	*Title XX*
Eligibility criteria . . .	Homebound; need skilled care; need certification by physician.	State can use homebound criterion; not limited to skilled care; need certification by physician.	Vary from state to state.
Payment to provider .	Reasonable costs.	Varies with state.	Three modes of payment possible: (1) direct provision by government agency; (2) contracting with private agency; (3) independent provider.
Services covered	Home health, skilled nursing, physical or speech therapy as primary services. Secondary services (social work and home health aide) available *only* if primary is provided. Position of occupational therapy in service hierarchy ambiguous.*	Limited home health mandatory; expanded home care optional; personal care in home optional.	Wide variety of home services allowed including: home health aide, homemaker, chore, meal services.
Percent of program dollars spent on home care	2%	0.1% to 0.5%	10% to 15%

*Occupational therapy was authorized as a primary service beginning in July 1981, but, as of October 1981, it has become an "extended" secondary service, which may continue if needed after primary services are discontinued.

TABLE 3.—*In-Home Care Expenditures and Beneficiaries (Fiscal Year 1977)**

Program	*Expenditures ($ millions)*	*Beneficiaries (in thousands)*
Medicare	458	690
Medicaid	179†	300
Title XX	491‡	489

*From US DHHS, HCFA: Home Health and Other In-Home Services: Titles XVIII, XIX, and XX of the Social Security Act: A Report to Congress. Washington, DC, Government Printing Office, no date (mimeo).

†State and federal.

‡Federal, state, local and private.

proportion varied from state to state but was generally less than 1 percent. New York state has the highest proportion of program dollars spent for home care: 4.4 percent. Title XX shows similar variability at a higher level (almost ten times that for Medicaid). In fiscal year 1978 California had the highest proportion of expenditure of Title XX funds for home services: 30 percent.[1]

Looked at another way, the magnitude of the various federal programs for home care suggests that Title XX and Medicare play a larger role than Medicaid (see Table 3). If one uses total expenditures, the largest pool of funds comes from Title XX. The largest number of beneficiaries served is covered under Medicare, but the numerous restrictions have the effect that Medicare's home health services are largely for persons who are acutely ill. It is indeed possible that some beneficiaries receive coverage under more than one program.

To illustrate the variation in Medicaid coverage of home health services, Table 4 summarizes elements of the programs as implemented in a selection of western states. Arizona is conspicuously absent because it does not have a Medicaid program.

Nursing Homes

The largest expenditure for long-term care, however, involves nursing homes. Often as a result of the perverse public payment system,[2] nursing homes continue to dominate the scene. Almost 40 percent of total Medicaid expenditures and about 75 percent of Medicaid expenditures for the elderly go for nursing home care. Thus, this type of care has emerged as essentially a welfare program.

As shown in Figure 1, the funding of nursing home care is very different from that for health care in general. The predominant role played by

TABLE 4.—*Characteristics of Medicaid Home-Health Programs**

State	*Home-bound*	*Skilled Care*	*Prior Authorization*	*Limit No. of Visits*	*Optimal Services*†				*Eligibility*‡			*Provider Supply*		*Reimbursement*§		
					PT	*OT*	*SP*	*AUD*	*CN*	*MH*	*BI*	*Total*	*Proprietary Number*	*Method*	*Cost/Nursing Visit*	*Certificate of Need*
California	x	x	>1 evaluation visit/6 weeks	..	..	..	..	..	x	x	x	111	36	Max	$26.10	..
		Postinstitutional care														
Colorado	..	..	....	150	..	..	..	..	x	..	x	32	0	LCOC	$28.00	..
Hawaii	..	..	SP, AUD	..	x	x	x	x	x	x	x	6	1	Medicare upper limit	$25.25	Yes
Idaho	..	..	....	..	x	x	x	x	x	..	..	11	2	UCR	$15.00-$30.00	..
Montana	..	..	PT, OT, SP	200/yr	x	x	x	..	x	x	Part B	15	0	Cont	$11.46-$28.00	Yes
Nevada	..	..	....	..	x	x	x	x	x	..	Part B	6	2	C-B	$27.13	..
Utah	x	..	Supplies>$100	..	x	x	x	x	x	x	Part B	9	0	Cont	$14.00	..
Washington	..	..	>$350 cost/mo	..	x	x	x	..	x	x	Part B	26	0	Max	$32.90	..
Wyoming	x	..	....	..	..	..	..	..	x	..	..	14	0	LCOC	$30.10	..
		Supplies limited to those available through a home-health agency														

*From US DHHS, HCFA: Home Health and Other In-Home Services: Titles XVIII, XIX, and XX of the Social Security Act: A Report to Congress. Washington, DC, Government Printing Office, no date (mimeo).

†Optimal services: PT=physical therapy; OT=occupational therapy; SP=speech therapy; AUD=audiology.

‡Eligibility: CN=categorically needy: Persons who generally meet income resource or other standards for Supplemental Security Income (SSI) or state supplementary payments under SSI or Aid to Families With Dependent Children. MN=medically needy: Persons who would be categorically needy except for their slightly higher income and/or resources, but who, in the view of the state, cannot afford to pay their medical bills. BI=buy-in: Persons who are members of a state's Medicaid coverage group who are also eligible to enroll in Medicare Part B.

§Reimbursement: Max=maximum allowance: Maximum amount established by the state for given product or service; state pays lower of actual charge or maximum allowance. Cont=contract: State purchases goods or services through a contract mechanism and pays the amounts specified. UCR=usual, customary and reasonable: An amount based on a provider's costs, such as annual operating costs. C-B=cost-based: State pays for services based on periodic allowable provider costs, such as annual operating costs. LCOC=lower of costs or charges.

Medicare in the funding of acute care is not seen in nursing home coverage, where Medicare is responsible for only about 2 percent of the total bill. Most public funds come from Medicaid. In 1976 almost 60 percent of all days spent in nursing homes were financed either totally or in part by that program.[2] But the figure does not show the dynamics of the situation. Almost a third of the patients who eventually become Medicaid patients enter as private-pay patients. Studies have shown that as many as two thirds of the group entering nursing homes as private-pay patients convert to Medicaid status some time during their stay. Of those who entered on Medicaid status, a third went on Medicaid at the time of admission.[2] This growing dependence on Medicaid is a particular problem because such status reduces the patient's chance of ever returning to the community. To get on Medicaid, the patient has had to spend away or sign away most of his assets. He thus has fewer resources on which to draw, were he to leave the nursing home.

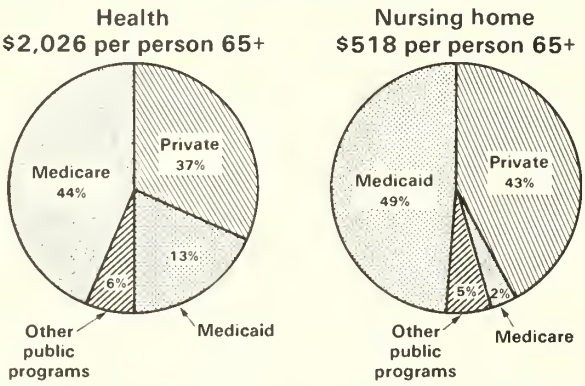

Figure 1.—Sources of health and nursing home expenditures.

TABLE 5.—*Comparison of Payment Sources for Nursing Home Residents and Discharges**

Primary Source of Payment	*1977 Residents*		*1976 Discharges*	
	Percent Covered	*Average Monthly Charge ($)*	*Percent Covered*	*Average Monthly Charge ($)*
Own income or family support	38.4	690	37.5	747
Medicare	2.0	1,167	17.0	1,300
Medicaid				
Skilled	20.0	873	18.0	767
Intermediate	27.0	610	17.1	597
Other government assistance or welfare	6.4	508	3.8	524
All other sources†	5.3	440	6.6	462

*From US DHHS, PHS, NCHS: The National Nursing Home Survey: 1977 Summary for the United States (PHS 79-1794). Vital and Health Statistics Series 13, No. 43. Hyattsville, MD, NCHS, 1979.
†Includes Veterans Administration.

Payment sources for nursing home care are illustrated in Table 5. The data, drawn from the 1977 National Nursing Home Survey, contrast the payment for residents with that for patients discharged. Several differences underline the dynamic nature of the nursing home population. In contrast to commonly held stereotypes about nursing home patients, the turnover for many patients is relatively rapid.[3] Again, data from the 1977 National Nursing Home Survey indicate that a third of nursing home patients are discharged within a month and more than half within three months. (In both cases, almost 80 percent are discharged alive.) Therefore, it is often critical to distinguish between reference to nursing home patients in terms of a cross section of residents or a cohort of admitted or discharged patients. The latter are made up of about equal numbers of long-stay and short-stay patients, while the former are predominantly long-stay. Some of these differences are apparent in Table 5 and account for the much greater role of Medicare in the coverage of discharged patients than residents and the correspondingly smaller proportion of that care provided by Medicaid and other government assistance programs. Similarly, one might conclude that the discharges were more likely to represent patients with somewhat more intensive care because their costs (other than those covered by Medicaid) tended to be higher than those for residents almost a year later.

We understand less about the factors that predict a patient's likelihood of entering a nursing home. We have progressed beyond what is now called the "5 percent fallacy," the simplistic statistics that report that approximately 5 percent of the population older than 65 are in a nursing home at any one time. As a first step, we can appreciate the heterogeneity of this distribution, made up of only 1 percent of those aged 65, 6 percent of those about 75 years old and more than 20 percent of those 85 years or older. From a longitudinal perspective, merely by looking at deaths we can show that 20 percent to 25 percent of persons aged 65 or older die in a nursing home.[4,5] By longitudinally following aged cohorts, investigators suggest that the proportion of elderly people who spend some time in a nursing home may be as much as 40 percent.[6,7]

But it is less clear how to identify those most likely to be admitted to nursing homes. Such an issue is critically important when we discuss the use of community services to replace or delay the

use of nursing homes. At the most basic level, we note that, compared with persons living in the community who are 65 years of age or older, nursing home residents are overrepresented by unmarried, white females. A government report comparing the disability of nursing home and community residents has been used as the basis for the often-cited statistics that for every person living in a nursing home, there are three equally disabled persons living in the community.[8] Such an observation, if correct, would strongly endorse the critical role of social supports (primarily informal, unpaid support systems like family and friends).[9,10] However, there have been substantive criticisms of both the methodology employed in the comparison[11] and the measures used to assess disability.[12] Nonetheless, social support has recurred in several studies as an important predictor of a person's likelihood of avoiding admittance to a nursing home.[13,14]

Trying to identify factors that predict an elderly person's likelihood of entering a nursing home is not encouraging. Few consistent patterns emerge. Weissert[15] could explain little of the variance in nursing home days using a combination of demographic (such as age, sex, race and marital status) and functional variables (such as mental functioning, physical functioning and diagnosis). In contrast, McCoy and Edwards,[14] looking at aged welfare recipients, found the probability of institutionalization associated positively with functional impairment, advanced age, household isolation, presence of nonrelatives and white racial background. Admittance to an institution was less likely in the presence of frequent contacts with friends and relatives and the propinquity of children.[14]

Coordinating and Managing Services

The complexity of the programs under Titles XVIII, XIX and XX of the Social Security Act, the unpredictable array of services that may be available through the Area Agencies on Aging, and the host of other public, voluntary or proprietary services that could be arranged for a patient needing long-term care defy ready description. Let us consider for a moment the patient's need rather than the characteristics of the largest programs. An older patient with multiple functional impairments may need, in addition to prompt diagnostic and therapeutic health services, lodgings suitable to his condition, meals, cleaning services, laundry assistance, personal nursing, transportation, confidence that help will be available in an emergency, companionship, mental stimulation and, perhaps, economic assistance to purchase other items.

Two points are important when one compares a patient's needs with the array of services available in a particular community. First, the ability to pay by no means insures that patients and their families will be able to identify and piece together a package that maintains their independence. Second, even though the legislated programs we have reviewed include a range of home services, the availability of such services is far from universal. Although one-stop shopping is rarely available, in most urban areas services can be mixed and matched until the patient is quite well outfitted. In many rural and surburban areas, the inventory of services is more threadbare and, to continue the metaphor, the outfit may need to be creatively and patiently stitched together for each client.

The physician alone need not shoulder the burden of arranging for social and health-related services for his office patients or care for his hospital patients after discharge. Indeed, the physician sensitive to the needs of geriatric patients and the peculiarities of the resources will draw on other expertise often and early. For patients in hospital, social workers need to begin the discharge-planning process early; service packages take time to arrange, often including discussions with family members regarding who may need to supply some of these services. From the physician, the social workers need to know the actual and anticipated functional limitations of the patient and the nature of the ongoing medical regimen. It is equally critical that private-pay patients as well as those near poverty level receive referrals to hospital social services when long-term care is necessary. Too often those patients who might be best able to use some of their own funds to sustain a preferred residency in the community believe that they have no alternative to institutional placement. Many posthospital patients (such as those with fractured hips or strokes) reach a point where they have received maximum benefit from acute care and are eligible for Medicare's 100 days of skilled nursing home care. At that point, counseling and joint planning with the patient can lead to a home care solution or to a planned short-term use of a nursing home; the latter requires that the patient and his or her family not foreclose

options to return to the community by closing up apartments and taking other irrevocable steps.

The physician may observe gradual deterioration in the functioning of a patient living in the community and often the patient's relatives are at their wits' end. Here, too, it is possible to make a referral to a community resource. A Visiting Nurse Association, the local health department or a Multipurpose Senior Center is a good place to start. Physicians should also be aware of the demonstration projects currently under way in many communities that provide a case management function. Such demonstrations take advantage of waivers of Medicare or Medicaid rules to bypass eligibility rules or provide an expanded array of services not usually covered. Essentially, the case manager assesses a client's needs and attempts to introduce a flexible service plan, sometimes cutting across usual program lines. In California, for example, the Multipurpose Senior Services Program offers case management to limited numbers of clients in eight different communities. It is critical that physicians, who tend to be the first line of defense against long-term care problems, be aligned with such community-based case management efforts.

The Physician's Role

Because so much of long-term care is cast in a medical mold forged by federal programs, the physician's role is pivotal. A physician's order, or at least concurrence, is a prerequisite to Medicare and Medicaid funding of many nonphysician services. A patient cannot receive nursing home or home care funding by these programs without a physician's request for these services. The physician is sometimes placed in a difficult position; he recognizes the patient's need for service, but the eligibility criteria may not fit the situation. He is tempted then to misrepresent the patient to make the patient's circumstances conform to an imperfect system. The need to find sufficient medical justification to put in place services to meet evident social needs has led to a great deal of frustration.[16]

The physician's critical role imposes another responsibility. Labels applied too readily may lead to deleterious self-fulfilling prophecies. For example, in the case of psychiatric diagnoses, treatable causes should be carefully sought before elderly patients are dismissed as senile. Once patients are treated as senile, it is all too easy for them to adapt by becoming senile. Even highly functional persons once admitted to psychiatric facilities have great difficulty getting out again.[17] With the elderly, the danger of iatrogenic effects is especially severe. The zone between therapeutic effectiveness and complications of therapy is treacherously narrow.

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Policy Shifts and Their Impact on Health Care for Elderly Persons

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Three major shifts in federal policy have been initiated recently that will directly affect the medical care of the elderly: (1) A significant reduction in federal expenditures for domestic social programs; (2) decentralization of program authority and responsibility to states, particularly through block grants; (3) deregulation and greater emphasis on market forces and competition to address the problem of continuing increase in the costs of medical care.

The federal policy shifts come at a time when many state and local governments are experiencing fiscal strain or fiscal crisis due, in part, to the rapid rise in expenditures for medical care for the poor and the imposition of limitations on, and even reductions in, tax revenues.

In the short term, changes at the state level, particularly limitations on Medicaid expenditures, are likely to have the most profound effect on medical care for the elderly. These changes will most likely include reductions in Medicaid eligibility and in scope of benefits as well as tight controls on hospital, nursing home and physician reimbursement.

NOT SINCE the debate on Medicare has federal policy affecting the elderly attracted so much attention. The changes in federal domestic social policy have been described as "massive," "revolutionary" and "drastic." Although the changes may seem to be dramatic and of very recent origin, they are, in fact, rooted in changes in the economy and public policy that began more than a decade ago.[1] In examining the potential effects of changes in the economy on physicians, on medical care, and on research and teaching, Fuchs observed that the likely impact of current trends will be a reduced flow of funds for patient care, research and training in the 1980's.[2] Blendon and coworkers stated that the decreased rate of economic growth in the 1980's will have a disproportionate impact on public expenditures, including those for health care, and they predicted an era "of challenge and stress for America's health institutions."[3] Geiger, who observed that conditions for the elderly have grown worse since the mid-1970's, noted that "social policy currently portends a decade of disaster for the health of older Americans, regardless of our ultimate actions in the area of medical care."[4]

The impact of changes in the economy and changes in federal policies that are attracting so

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ABBREVIATIONS USED IN TEXT

AFDC = Aid to Families With Dependent Children (program)
FY = fiscal year
GNP = gross national product
HMO's = health maintenance organizations
SSI = Supplemental Security Income (program)

much attention can be viewed from the standpoint of individual persons or groups of persons who are affected, programs and institutions, local and state governments, or areas of the country (for example, the Northeast may be more severely affected than the Southwest).

Although many policymakers, policy analysts and health professionals view the shifts—particularly the budget cuts in domestic social programs—as essential to combat inflation, they seem less certain about the impact of these shifts on services for those who are largely dependent on public programs and institutions that provide those services. This uncertainty exists because there have not been detailed analyses of the federal policy shifts in relation to the growing fiscal problems in many state and local jurisdictions.

Our own studies in health and aging policies during the past decade have convinced us that the next few years will be difficult, challenging and troubled times for the elderly and for those who provide medical care for this population. The problems arise mainly because of the continued rapid increase in the cost of medical care, particularly hospital care, and the fiscal crisis that is affecting local, state and, now, the federal government.

In this paper we will discuss three major federal policy shifts that will affect medical services, including long-term care for the elderly. We will examine these policy shifts in relation to the concepts of fiscal crisis and decentralization. Not only will access of older persons to medical care be affected by the changing policies, but physician-patient relationships and the capacity of the independent sector (nonprofit), public and profit-making institutions to provide necessary services may be vitally affected as well.

The three major shifts in federal policy that will directly affect the medical care of the elderly are (1) a significant reduction in federal expenditures for domestic social programs; (2) decentralization of program authority and responsibility to the states, particularly through block grants; and (3) deregulation and greater emphasis on market forces and competition to address the problem of the continuing increase in the cost of medical care.

A fourth policy development of major importance, the Economic Recovery Tax Act, may have many indirect effects on health care for the elderly, but these will be mediated largely through philanthropic contributions to independent (nonprofit) sector institutions. These are difficult to gauge at present. Two of the policy initiatives have already been adopted by congress in the Omnibus Budget Reconciliation Act of 1981 and signed into law by the President. The cuts in federal spending and the decentralization of program authority to the states spelled out in the act respond to problems (for example, fiscal crisis) and build on policies (such as new federalism) that began to emerge in the early 1970's. We believe that the fiscal constraints at the state and local levels will have a more dramatic effect on medical care for elderly people who are poor than will the federal policy shifts.

The Concept of Fiscal Crisis and Reduced Federal Expenditures

Fiscal crisis is a concept that has had a major impact on the policies of local and state governments. In the past the term fiscal crisis had been used to describe the problems of a local government that could not service its debts (for example, New York City and Cleveland) or of a state whose expenditures exceeded its revenues. The term fiscal crisis is now being applied to federal expenditures for social programs.

Since 1975 there has been a decline in federal, state and local expenditures as a percent of the gross national product (GNP) and a decline in per capita expenditures in constant dollars.[5(p4)] After intergovernmental transfers (such as federal and state to local, or federal to local), the most significant declines are at the local level.[5(p6)] Since 1975 state and local expenditures have declined from 15.1 percent to 13.5 percent of the GNP, while federal expenditures have decreased from 12.3 percent to 11.9 percent of the GNP.

The fiscal problems are further compounded by the fact that there are five different classes of local governments competing for increasingly limited funds: counties, municipalities, townships, school districts and special districts. In most states, the counties and municipalities are primarily responsible for health and hospital services, but in

some states, special hospital districts also play an important role. Competing for these limited funds are education, public welfare, highways, police, fire, corrections, sewage and other sanitation services, housing and urban renewal, parks and recreation, government administration and, increasingly important, interest on government borrowing.

Fiscal crisis at the local level will be exacerbated because of the severe cutbacks in direct local federal aid. The community development block grants and the comprehensive employment and training block grants have been eliminated, and others have been significantly reduced.[6]

Two issues link fiscal crisis and health care for the aged: (1) the escalation in expenditures for medical services for the elderly, partly due to increased access and increased numbers of older people, but primarily due to the rising cost of medical services, and (2) the imposition of limitations on, and even reductions in, revenues for such services at the state and local levels.[7,8] While costs are escalating there are definite limits on funding for health and social services.

From above there are (1) federal limits on Medicaid expenditures and (2) major block grant initiatives with a 25 percent reduction in the funding level of the prior categorical programs that the block grants replace. Both of these conditions are shifting medical care costs to the states, to local governments and to the elderly themselves.

From below there are fiscal crises and tax revolts at the state and local levels. Caught in the squeeze, health and social services are involved in a "fiscal crisis" of their own. During the 1980's all levels of government will seek to cut costs and shift expenditures to other jurisdictions. For example, at least half of the states were planning Medicaid cuts before the enactment of the Omnibus Budget Reconciliation Act of 1981. Many more will follow suit as a result of the limits that the act placed on the federal share of Medicaid costs.

These fiscal pressures at multiple government levels pose a particular problem for Medicaid-funded services because of the magnitude and rapid increases in these expenditures, now outrunning the capacity of states to raise the necessary revenue.[9] In view of the Medicaid expenditure escalation (Medicaid costs have risen more than 500 percent between 1968 and 1978, from $3.5 billion to $18 billion), and the fact that 20 percent of the elderly receive Medicaid and 39 percent of Medicaid expenditures are for the elderly, the cost-containing policy changes at the state level are likely to affect the elderly directly. The federal Medicaid expenditure limitation* and the difficulty that many states face in funding Medicaid will require (1) a major effort by the states to contain costs in the Medicaid program itself and (2) policy modifications in other state benefits that could directly and adversely affect health care for the elderly.

Long-term care services for the elderly will be affected in several ways: reductions in supplementary income support—such as reductions or elimination of state supplementation or cost of living increases in Supplemental Security Income (SSI) benefits for the poor elderly; and reductions in such social services as state supplementation of vitally needed homemaker, home health and adult day health services under Title XX of the Social Security Act (this has been cut 25 percent, from $2.9 billion to $2.4 billion, under the Social Services block grant).

The Omnibus Budget Reconciliation Act includes a number of provisions related to Medicare and Medicaid that are expected to reduce federal expenditures for these programs in fiscal year (FY) 1982 by $2.5 billion. The 3 percent reduction in the federal share of Medicaid expenses is only one of these policy changes. Among the more important Medicaid policy changes are (1) states are given greater flexibility with respect to coverage of and services for the medically needy, (2) states no longer need to reimburse hospitals at the Medicare rate, (3) the freedom of choice provision of the state Medicaid plan can be waived by the Secretary of Health and Human Services and (4) participation in health maintenance organizations (HMO's) is encouraged.

The Medicare policy changes in the Omnibus Budget Reconciliation Act of 1981 increase significantly the copayments and deductibles paid by older persons. The Part B deductible was raised from $60 to $75 per year. The Part A deductible for those admitted to hospital was increased from $204 to $250 (it had been scheduled to rise to $228); in 1984 it will be $328. The coinsurance for extended care in hospitals and skilled nursing facilities was also raised.

Although appearing to be small, these increases

*In fiscal year (FY) 1982 the federal Medicaid expenditure limitation will be 3 percent below the FY 1981 formula requirement; in FY 1983 it will be 4 percent below and in FY 1984 it will be 4.5 percent below the present formula.

become significant when viewed in the context of the rapidly rising out-of-pocket costs that are already borne directly by the elderly, estimated to be in excess of $1,000 per capita in 1979, and the increasing rate of poverty among this population. The other major changes in Medicare and Medicaid are primarily in hospital reimbursement. These changes will reduce current levels of Medicare and Medicaid reimbursement for hospitals.

In attempting to contain Medicaid costs, at least six options are available to state governments: (1) reducing Medicaid eligibility, (2) reducing the scope of benefits, (3) holding reimbursement for hospitals, nursing homes or physicians at current levels as costs rise, (4) improving program management to reduce fraud and abuse, to reduce use, particularly of hospital services, and to eliminate inappropriate payments, (5) initiating delivery system reforms (for example, HMO's and vouchers) and (6) initiating program restructuring (such as long-term care block grants).

Our own and others' research indicates that several states have already begun to reduce the level of benefits and to restrict Medicaid eligibility. Two of the biggest items (and most likely targets) for Medicaid cost cutting are (1) reducing or eliminating eligibility for the "medically needy" and (2) reducing optional benefits, including intermediate care nursing home benefits. At the same time, hard-pressed cities and counties have been closing neighborhood clinics, hospital outpatient departments and other services, as well as restricting eligibility for city- or county-provided services.

If the medically needy Medicaid category now established by many states were limited in eligibility, many older persons would be removed from eligibility and would not be able to obtain needed services such as nursing homes, home care, and hospital and physician services or they would be forced to pay for these services out of pocket. Many of these elderly patients are in nursing homes at the time they become eligible for Medicaid. They have "spent down" their income and assets to a level that qualifies them for Medicaid. Reducing the income and asset requirements even further will shift the costs to the elderly and their families—many of them hard pressed or unable to meet the costs of such care.

Another approach to reducing Medicaid eligibility, which the states might initiate, would be to hold requirements to the level established for the previous years, while inflation continues to increase costs for food, housing and medical care. Spitz and Holahan and many others have advised that cutting back on Medicaid eligibility as a cost containment strategy may have unanticipated negative cost implications, such as shifting costs from one program to another or transferring costs from state to local government.[10,11] Although such a strategy may save the federal or state governments money, local governments may not be able to meet these demands. During recent years, the number of Medicaid eligibles has declined by almost 3 million, largely due to the failure of states to adjust Aid to Families With Dependent Children (AFDC) eligibility (thus Medicaid eligibility) to inflation.

Another likely method for states to control Medicaid costs would be to reduce or eliminate optional benefits (such as prescription drugs, intermediate care facilities, dentistry, physical therapy, prosthetics or optometry). There is little evidence that cutoff of certain optional benefits, such as prescription drugs, will reduce costs because some patients may have to be admitted to hospital to receive the necessary drug treatment. In such cases, the impact of eliminating some optional benefits may be to increase the overall program costs. Because the optional benefits of prescription drugs, dentistry and prosthetics constitute a minor portion of the overall budget and the cost increases of the Medicaid program, eliminating such programs may not reduce the Medicaid budget. And most important, the cutoff of optional benefits will affect those with the most chronic illnesses disproportionately, making them suffer the greatest hardships.[10,11]

Among the other alternatives, the most likely to have an immediate impact are reducing hospital, nursing home and physician reimbursement as well as further restricting Medicaid patients in their choice of private practitioner, community hospital and nursing home. These changes may be the ones most strongly resisted by the medical lobbies because the American Medical Association has indicated its preference for cuts in eligibility rather than cuts in reimbursement.[12]

Improved program management, including prior authorization for elective hospital admissions, utilization review, fraud and abuse control, audits and other management techniques have already been adopted in many state Medicaid

programs. It is unlikely, in our view, that these will produce sufficient short-term savings to compensate for the rising costs of medical care and the reductions in the federal share of expenditures. Delivery system reforms are also unlikely to be initiated soon enough to have a substantial impact on Medicaid expenditures in the next few years. They are much more likely to be encouraged for patients with private health insurance or Medicare coverage. Finally, program reforms, such as long-term care block grants, are likely to be considered but are unlikely to deal with the fiscal crisis in the short run.

The largest problem with the federal Medicaid spending limitation is that, in itself, it does nothing to address the source of rising medical care costs, particularly the increase in hospital costs. It merely shifts to the states the difficult and politically treacherous decisions about how to deal with those costs and the resultant public expenditures. Further, there has been little consideration of the possible cost shifts that the new Medicaid expenditure policy will generate—for Medicare or for programs funded by the state (such as SSI supplements and social services for the elderly).

There has been no published analysis of the possible consequences of the federal limitation on Medicaid for the Medicare program. Such an expenditure shift could occur, for example, if patients who are no longer eligible for nursing home coverage (because of Medicaid spending limits) are kept (at Medicare expense) for longer hospital stays than would occur if Medicaid nursing home coverage were available.

Decentralization and Block Grants

Budget cuts have also been made in the block grants, which represented the second major element in President Reagan's domestic social program proposals. In the 1970's this policy concept emerged under the banner of "new federalism," which converted several categorical programs to block grant type revenue-sharing programs (for example, Title XX of the Social Security Act). Designed to decentralize responsibility for domestic social programs to state and local governments through block grant type funding and to limit federal involvement in those programs, new federalism boosted the fiscal and political responsibility of state and local governments for multiple programs, including those affecting health care.[13] Both the block grants of the 1970's and those created in the Omnibus Budget Reconciliation Act of 1981 ease the constraints of categorical funding and of federal requirements, resulting in increased discretion for state government decision-making in multiple programs that affect the elderly, including such health programs as community mental health centers, home health services, emergency medical services and hypertension control.

An important consequence of the block grants is that the wide discretion that they provide the individual states fosters great inequities in the same program across the states. This, in turn, makes it impossible to assure uniform benefits for the same target population (for example, the aged) across jurisdictions or to maintain accountability with so many varying state approaches. Finally, because the most disadvantaged are heavily dependent on state-determined benefits, they are extremely vulnerable in this period of economic flux.

The net result of the large-scale shift to block grants in health and social services, combined with the across-the-board 25 percent reduction in FY 1982 federal expenditures for the block-granted programs, is increased pressure on state and local governments to underwrite program costs at the same time that many states, cities and counties are under great pressure to curb rising expenditures. The result is likely to be serious for elderly poor people in many communities.

Deregulation and Stimulation of Procompetition Market Forces

The third major policy initiative is deregulation and stimulation of procompetition market forces. These strategies are based on the assumption that market forces can produce an effective competitive medical care system and that the present system is not competitive except in ways that increase costs. Two distinct market structures have been proposed to meet the requirements of a competitive system: (1) the cost-sharing approach (large front-end deductibles and coinsurance) based on provider price competition over service price and (2) the health plan approach (such as health maintenance organizations and other plans that provide specified benefits for a population at a fixed premium through various practice arrangements). Although physicians, hospitals and others involved in medical care favor deregulation, there

is growing concern about and opposition to some of the procompetition proposals that are likely to be advocated by the Reagan administration. The writings of Enthoven and others give a clue to what these policy proposals will include.[14-16] The "competition strategy" described by Enthoven refers to the proposed application of the following four principles in health care financing: (1) multiple choice—each consumer would be offered the opportunity to enroll each year for the coming year in any of the qualified plans for health care offered in the area; (2) fixed dollar subsidy—each consumer would receive a fixed dollar subsidy (by his or her employer) toward the purchase of a health plan membership; (3) use of the same rules for all competitors would govern premium setting practices, minimum benefit packages, catastrophic expense protection and so on, and (4) organization of physicians into competing economic units, which could include group practices or other organizational arrangements, would be required.

Several procompetitive proposals have been introduced in the 97th Congress, including H.R. 850—National Health Reform Act of 1981 (Representative Gephardt); S. 433—Health Incentives Reform Act (Senator Durenberger), and S. 139—Comprehensive Health Care Reform Act (Senator Hatch). The Reagan administration has also indicated its intention to propose procompetitive legislation during this congress.

Although the bills differ in detail, there are several elements that characterize the procompetitive approach. These are (1) changes in tax treatment, for employers, employees or both, regarding employer contributions to health insurance plans; (2) establishment of incentives or requirements for employers to offer employees multiple choice of health insurance plans subject to certain limitations with respect to coverage of services and cost sharing, including catastrophic benefits and preventive care, and (3) establishment of Medicare and Medicaid voucher systems under which elderly, disabled, blind and AFDC-eligible persons would receive a fixed value voucher that could be used toward the purchase of a qualified health insurance plan.

One proposal being considered by the Reagan administration would provide Medicare-eligible persons with a voucher—initially worth perhaps $1,700 (average Medicare cost at present)—with which they could purchase private health insurance. The voucher plan may also include the provision that beneficiaries may opt to retain current Medicare coverage and that no voucher-eligible private plan can provide less coverage than Medicare itself. It is impossible to predict or provide an analysis of the likely consequences of this voucher proposal because few details of the administration's proposal have been made available. The voucher is, potentially, a mechanism for capping federal Medicare expenditures and shifting the financial risk to the individual patient. These elderly people might control expenditures by selecting a health insurance plan with the minimum required benefits.

The voucher may be a viable alternative for relatively healthly older people, particularly those who do not have chronic illnesses that require extensive medical and hospital care. However, for those with serious chronic illnesses and disability, particularly the poor, the picture is different. They may not be able to enroll individually in a plan that can meet the high costs that their care may entail. This is particularly true for the medically needy elderly who are in skilled nursing facilities or intermediate care facilities.

Much of the impetus for the procompetitive proposals comes from the success of health maintenance organizations in reducing costs for their controlled populations and for stimulating competition among providers in the fee-for-service sector. The picture is not that simple, as our colleague Harold Luft has pointed out.[17,18] It is clear that medical care costs for HMO enrollees are 10 percent to 40 percent lower than those in conventional plans. The factors that account for this reduced cost are less clear. It is evident that HMO's dramatically reduce hospital admissions, and for those in hospital, the length of stay and the use of services are slightly reduced. It is not clear whether part of the reduction in hospital use is due to (1) the particular consumers who select HMO's, (2) the group practice organization, (3) the lack of financial incentives for physicians to admit patients to hospital or (4) the more conservative practices of HMO physicians. A recent study comparing utilization patterns in a large multispecialty, primarily fee-for-service group practice and a prepaid group practice suggests that the group practice organization itself may be a critical factor in reducing hospital adminissions.[19]

In analyzing the limited role that HMO's have

played in the care of the elderly, Harper, Butler and Newacheck[20] examined the factors that may influence HMO efforts to attract older patients, the factors that may stimulate older persons to consider joining HMO's, and the formidable obstacles to HMO enrollment of the elderly, particularly Medicare reimbursement of hospitals, the relationship of elderly patients to fee-for-service physicians, and people's reluctance to change to a new form of care. The authors concluded that without any change in Medicare policy, HMO growth in serving the elderly will take place slowly. This is an area that has been explored in only a few policy studies.

Two other approaches to cost containment strategies—also labeled procompetitive—have been proposed during the past decade. One of these approaches resembles Enthoven's strategy in that it attributes a large share of increases in health care cost to the spread of third-party coverage for the costs of care. This theory, which has been advanced by Feldstein,[21] Pauly and Seidman,[22] has been increasingly accepted as a major factor contributing to rising costs. The lack of incentives for provider and consumer restraint led Feldstein to propose that third-party coverage should be limited to catastrophic costs and that transactions between patients and physicians in day-to-day care should be subject to normal competitive market forces.

The other procompetition strategy, advocated by Havighurst and the Federal Trade Commission, is basically an antitrust strategy aimed at providers.[23] Advertising would be encouraged, and collusion among providers and other forms of illegal behavior would be prohibited. Again, the stress is on the market and on permitting it to function in a traditional fashion.

In view of the procompetitive proposals—particularly those using vouchers and changes in tax policy—that are likely to emerge as public policy in the coming months, the best strategy would appear to be one of well-designed experiments coupled with careful monitoring of the medical care market to analyze the effects of alternative approaches on access, quality and cost, and reduction of disincentives to competition (such as tax subsidies to employers who purchase expensive health insurance plans for employees or current Medicare reimbursement policies); most informed observers believe that increased regulation will also be needed to stimulate competition. It is paradoxical that to stimulate competition, which may actually control cost increases, regulation must be increased.

In view of the recent federal policy shifts affecting health care for the elderly—particularly expenditure reductions, block grants and deregulation-procompetition proposals—we believe several steps are necessary. First, we believe it is necessary to initiate federal and state policy monitoring and policy analysis, as well as health services evaluation at the local level to assess the impact of the policy shifts on state and local governments, on providers, on the elderly and on other groups dependent on public programs and institutions for needed services. Because of the importance of independent sector (nonprofit) institutions in providing services for the elderly, we believe it is particularly important to assess the impact of federal and state policy changes on these institutions and on the elderly whom they serve.

These are indeed times of change and challenge for physicians and health care institutions and for the elderly they serve. To meet the formidable challenges ahead, physicians must be better informed about the impact of public policies on health care for the elderly; further, they must examine more critically what can be done within medicine to meet the health care needs of those with chronic illnesses and disability, particularly elderly patients. We believe, as do many others, that the resources devoted to health care are ample to meet the needs, but they will not be if we continue down the path that medicine has followed for the past 30 years.

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EDITORIALS

The Elderly as Interdependent Persons

As the number of elderly persons continues to increase, the quality of life for this group of citizens assumes growing importance. This special issue of The Western Journal of Medicine addresses many aspects of the aging process and contains up-to-date information on the medical care of older persons. Less clearly expressed, but nevertheless running through many of the articles, is the notion of interdependence—interdependence among the multiple ailments so often afflicting an elderly person, interactions and interdependence among multiple medications and with altered physiologic states related to aging. Also, there is more than a hint of an interdependence of elderly persons with one another and with the human and physical aspects of their care and their environment. Yet one senses that this notion of interdependence is missing, or at least not emphasized, in many present-day approaches to the care of the elderly. They seem more directed toward maintaining the independence of an oldster for as long as possible, but failing this to accept passive dependency as the more or less inescapable alternative. It seems that relatively little attention is being given to what might be thought of as a middle ground, the fostering of interdependency both to help sustain independence and to soften the indignity and perhaps even the cost of the more or less complete dependency that is the unhappy lot of so many of the nation's elderly today.

Quality of life and costs that can be borne are the central challenges to those in advanced years. These are very personal problems for older persons but they are also growing problems for society as a whole as the number of older persons has grown out of proportion to the rest of the population. A shortfall of resources to care for the elderly is predictable if it is not now here. These numbers are even now bringing about changes. It is evident that senior citizens will need to carry more of the burden of their own maintenance and care. Already there are opportunities and even pressures for more senior citizens to carry more of the costs of their own maintenance by continuing to work and be productive further into the latter decades of their lives. By the same token it is beginning to be evident that as resources become less affordable for society as a whole, the elderly may have to do more to help take care of each other, to enhance the quality of their lives and to help make the available dollars go as far as possible. What appears to be needed is to further strengthen community and interpersonal action by the elderly in behalf of the elderly and to foster increasing interdependence among them as a replacement for increasing dependence and decreasing quality of life.

In recent times American society, with its focus on nuclear families and a youth oriented culture, has tended to isolate the elderly both individually and collectively. But the trend now seems to be away from this isolation. Collectively, as their numbers have grown, senior citizens have begun to make their social, economic and political interdependence with society clearly evident. It is suggested that what may be needed now is to extend this focus and to view the elderly themselves as interdependent persons with something to give each other and to their local human and physical environment, and who together can do a great deal to enhance the quality of their care and their lives.

There is much in this issue of the journal that suggests that where interdependence can be substituted for both independence and dependence in the health care and attitudes of older persons, there can result an improvement in the quality of life in the declining years and there might even be some reduction in the costs of caring for this growing segment of the population as well.

—MSMW

Why Aging?

HUMANS HAVE BEEN INTERESTED in the phenomenon of aging throughout their existence and seemingly for two main reasons: the general and innate human curiosity about biological processes and the human fear of the unknown in dying. In fact, the aging process seems to have been responsible for the devotion of vast human resources to disease prevention and for the fact that organized Western religions promise personal escape from the fear of nonexistence following death. Accordingly, to explain aging, humans have proposed theories that range from Original Sin to the loss of the crucial substance "vitality," and finally to a recent proposal that aging is due to an intracellular accumulation of defective information—an hypothesis that is discussed by Charles Scoggin in "The Cellular Basis of Aging" in this issue.

It is not an easy chore to define aging or senescence. Aging obviously must be defined in terms of life and time. In most contexts the concept of time is based on velocity, and the direction of time determined by the second law of thermodynamics—that is, entropy as a measure of disorder. As time advances disorder increases. Thus, time breeds disorder in systems that are animate as well as those that are inanimate. In fact, life and death can probably be best defined in terms of entropy and equilibrium. The important point remains that aging is apparently due to an increased disorder in the system, which interestingly predicts that aging cannot occur at the temperature of absolute zero.

For a formal definition of aging one might use a modification of that proposed by Strehler[1]: "Aging is defined as the changes which occur in a living organism, generally in the postreproductive period, which temporally result in a decreased survival capacity and an increased vulnerability of the individual organism." Strehler further proposes four criteria for changes of aging: They must be *universal* (that is, occurring in all older members of the species), the changes must be *intrinsic* to the system (not due to environmental factors), they must be *progressive* and accumulate gradually rather than suddenly (this excludes strokes and myocardial infarcts as aging processes) and finally they must be *deleterious* changes (rather than, for instance, developmental or adaptive changes which do occur intrinsically and progressively in all metazoan organisms but which clearly are advantageous). With such a definition and the above criteria of aging, it is apparent that the ability of an aging or senescing organism to survive a challenge from its environment depends upon (1) the absolute magnitude of the challenge and (2) the magnitude of the resources available to the organism to offset the disruptive effects of the challenge. Inferred in this description of the organism's interaction is a claim by Peter Medawar that "No death is wholly 'natural'; no one dies merely of the burden of the years." While that claim may be true for humans, at least old horses come close to dying "merely of the burden of the years" as a direct result of the burden caused by edentation and, consequentially, death by starvation.

Students of genetics have raised the important question of why evolution has permitted senescence to occur. Is there a strong positive selective advantage of a finite life span, or is the selective pressure against senescence so weak that it has been ignored, or is senescence an unavoidable byproduct of the evolution of other advantageous characteristics? According to Orgel's "error catastrophe theory," briefly summarized by Dr. Scoggin, and the experimental evidence supporting it, the latter is likely the case. To this issue I should like to quote from an enlightened essay entitled "The Duration of Life" presented by August Weismann to a meeting of the Association of German Naturalists at Salzburg[2] 100 years ago:

> If by these considerations death is shown to be a beneficial occurrence, it by no means follows that it is to be solely accounted for on grounds of utility. Death might also depend upon causes which lie in the nature of life itself. The floating of ice upon water seems to us to be a useful arrangement, although the fact that it does float depends upon its molecular structure and not upon the fact that its doing so is of any advantage to us. In like manner the necessity of death has been hitherto explained as due to causes which are inherent in organic nature, and not to the fact that it may be advantageous.

It is apparent that whatever the nature of the aging process, its detrimental effects are generally circumvented by the process of gametogenesis and sexual reproduction in organisms prone to aging. In fact, one might conclude that the function of life is to perpetuate the germ line, a function carried out by the soma, a not infrequently awkward appendage.

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The Cellular Basis of Aging

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Normal cells have only a finite life span before they die. The process known as aging may occur as a result of continued damage to the cell or as a result of expression of predetermined information within the genetic structure of the cell. Both processes lead to progressive cellular dysfunction which is evidenced by the organs of the body as aging. By understanding how individual cells age we will gain insight into how the body as a whole ages. The impact of such knowledge on science and society is a matter of both conjecture and concern.

THE CHANGES of the body which occur with aging are well known. Wrinkling of skin, graying of hair, lessened muscular strength, and diminished sensory functions such as decreased vision and hearing are almost universal phenomena. Other consequences of aging are less predictable. For instance, many persons remain mentally sharp well into their 80's while others will display progressive dementia as early as the sixth decade of life. Because aging is a universal human experience it has been a constant area of scientific inquiry. The study of the basis of the process of aging has been termed "biogerontology."

The aging process is evident within the cells of the body. As cells age there is a decline in vital functions such as oxidative phosphorylation.[1] Studies of β-adrenergic receptors of cells show decreased adrenergic responsiveness.[2] Such findings may account for decreased ability with old age to tolerate stress and exercise. Decreased cellular production of molecules vital for function occurs with aging. DNA synthesis has been shown to decline appreciably in aging WI-38 fibroblasts.[3] RNA synthesis decreases in aging cells.[4] Incorporation of radiolabeled amino acids into proteins dwindles with age of the cell.[5] Interestingly, lipid synthesis is less affected by aging than production of DNA, RNA and proteins.[6] Since the cells make up the organs that constitute the body, changes in cellular function are reflected in alterations of the organs and body. This review starts from predication that the structural and functional basis of the somatic phenomena recognized as a consequence of aging lie within the cells of the body. Understanding how cells age will lead to insight into how the body as a whole ages. Certainly such knowledge of cytogerontology[7] should help us to deal with the consequences of aging. Whether or not such perceptions will eventually lead to measures to reverse or arrest the present inevitability of the process is speculation.

In general, it is thought that the changes associated with aging of cells may occur through two major mechanisms. Progressive damage to the cell, either from external or internal factors, may lead to accumulative cellular dysfunction which

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is manifest in the intact individual person as aging. The second factor which is of importance is the genetic information within the cell. While many theories have been proposed it is probable that there is no single cause of aging; therefore, both major mechanisms probably jointly contribute to the final process of aging.

Aging as a Consequence of Progressive Cellular Damage

It is possible that aging of cells may be the consequence of "wear and tear." This type of damage may arise as a result of damage from elements outside of the cell or by damage from factors within the cell. Most investigations have focused on damage to the DNA and protein mechanisms of cells.

Damage to Cells by External Environmental Factors as a Cause of Aging

It has been suggested that toxic factors within the environment may lead to progressive damage of the genomic information of cells. The possible effect of background irradiation is an example.[8] Background irradiation may act to damage chromosomes or single genes either mutating or inactivating them. Accumulated damage would eventually be expressed as absent or abnormal gene products. Alterations in normal gene function would lead to the changes of cellular activity associated with age. It has been proposed that as the errors of cellular function accumulate, they eventually summate to form the "error catastrophe" which results in death.[9] Some would speculate that many environmental factors may play a role in changing gene expression with age. While in the modern world infection plays a less prominent role, it is possible that chemical and other toxic factors within the environment may have a harmful effect on the genome of a cell. Thus, the effect of environmental stress would lead to progressive damage to cells, particularly the genes which are the primary source of information for cells, leading to the changes in the whole organism which we recognize as aging. However, it is important to stress that abnormalities of gene function have yet to be shown to be a correlate of aging in humans. Likewise, chromosomal changes have not been associated with aging in humans. In fact, changes of the chromosomal makeup of cells (aneuploidy) is an almost constant feature of cells with a seemingly infinite life span—malignant cells. Epidemiological association between exposure to environmental toxins, radioactivity or other factors that may alter cell function have not been established.

When suggesting that "wear and tear" may result in aging, it is not necessary to ascribe all the impact of "wear and tear" to be on the chromosomal and protein synthesizing mechanisms of the body. In areas of the body such as the angle of the jaw and elbows there is progressive loss of elasticity and thinning of the skin. The changes may just represent the consequences of usage. Unlike cells that are very active metabolically, the connective tissue that serves as a framework for tissue is relatively static. Thus the continuous extension and relaxation of the fibers may lead to progressive degeneration from the effects of such stress alone. Exposure to sunlight may accentuate such degeneration.[10]

Aging Due to Cellular Damage by Factors Internal to the Body

Certain products of metabolism toxic to cells may escape the normal cellular degradative processes. These factors may cause damage of cells which leads to the changes of age. This would be a process similar to gradual accumulation of harmful by-products of combustion in an automobile engine. With time, progressive dysfunction and eventual failure of the machine occurs. Two classes of substances are examples of this potential cause of aging in living organisms. Aldehydes bind to molecules such as DNA and enzymes to irreversibly inactivate them. It has been proposed that the increased cross-linking of collagen seen with aging is due to the effect of aldehydes.[11]

Free radicals of oxygen are another product of cellular metabolism that may damage biological tissues, and have been proposed as playing a prominent role in the aging process.[12] They arise from a number of reactions within cells and are a result of normal oxidative metabolism of organic compounds by molecular oxygen. The oxygen radicals which are produced include singlet oxygen, superoxide radical, hydroxyl radical and hydrogen peroxide. These oxygen species are highly reactive and can alter most types of cellular macromolecules. They have been shown to peroxidize unsaturated fatty acids, oxidize proteins, damage nucleic acids and cleave polysaccharides.[13] When these radicals are generated in the media surrounding cells in tissue culture, they can kill and lyse cells. We have found that hydrogen peroxide appears to be the primary oxygen

radical that causes fatal injury to human cells in tissue culture.[14] It is possible that the other radicals of oxygen play a more prominent role in the intracellular damage of human cells.[15] It has been suggested that in aging the progressive accumulation of damage from such reactive radicals may lead to diminution of cellular function and tissue integrity which we recognize as aging. It is to be emphasized that the possible roles of free radicals in the aging process remain speculative. It has not been shown that the level of free radicals increases with aging nor have the levels of free radicals been shown to be higher in animals with short life spans than in animals with long life spans.[16] Should, however, the effect of free radicals be substantiated, it would suggest some interesting therapeutic possibilities. This is because there would be possible ways to bolster cellular defense against oxygen radical challenge. Antioxygents such as vitamin E, superoxide dismutase, catalase and methyl sulfoxide might have benefit.[17] To date there is no scientific information to support the use of such compounds as panaceas against the aging process.

Genetic Predetermination to Aging

Regardless of the possible impact of factors from without or within that serve to damage cells, the normal cell itself has only a finite life span of approximately 50 doublings before it is no longer capable of replication.[18] This innate senescence cannot be overcome by placing the cell in a protected or "young" environment. Animal transplantation experiments have shown that transplantation of "old" cells into young inbred recipients does not change the cell life expectancy.[19] Furthermore, the determination of the finite life of cells appears to lie within the cell nucleus. Fusion of cytoplasm from young cells with nuclei of old cells (and vice versa) leads to a hybrid cell whose longevity is determined by the parent nuclei, not cytoplasm.[20] However, even though the number of replications of human cells is finite, it is probable that aging is not the result of cells losing their proliferative capacity, rather it has been proposed that within the human genome exists a predetermined program to progressively slow down or shut down the physiologic phenomenon of the body.[21] The information to do this may differ from cell-type to cell-type within the body. Individual differences may occur. In one person wrinkled skin may develop as an obvious manifestation of aging while dementia develops in another. Thus the genome would be much like a tape that plays out a scenario that we recognize as aging. The transition from youth to age would simply be a programmed translational event of our genetic information. A genetic link with aging is supported by studies of twins that show an hereditary influence on life expectancy,[22] and investigations that have demonstrated an association between the major histocompatibility complexes and aging.[23]

What Unifies Our Current Concepts of Aging?

As mentioned before, there is no one theory of aging that is universally accepted. There do appear to be some unifying features in the mechanisms discussed above. One feature is that genetic instability is a prominent cause of aging. While genetic predeterminism would make it inevitable that aging and eventual failure of the organism would occur, it is obvious that all individuals of a species within the same environment do not age at identical rates. We speak of "mean life expectancy" which is very similar to the term "mean time to failure" used by Hayflick.[21] What this implies is that the rate at which we age varies from person to person because the genetic tape is longer or shorter (thus the tendency of families to be long-lived or short-lived) or because its translation is either faster or slower.

But in addition, the ability of the body to withstand and repair damages either from within or without would also play an appreciable role. This is of clinical relevance to gerontology because it is foreseeable that we should be able to further influence longevity by decreasing the effect of or exposure to damaging substances. We may also be able to influence the ability of the body to repair itself. The longevity of our current population represents the impact of such approach. Sanitation, improved diet, chemotherapy of infectious disease and treatment of heart disease may be looked upon as factors that have decreased background noise and allow our genetic tapes to play a little longer. Whether or not we will be able to influence the genetic message directly is highly speculative; however, the future for research on the cellular aspects of aging is exciting.

What Are Some of the Perplexing Questions Remaining?

It is not known why variations in aging exist from species to species. It has been proposed that metabolic rate may account for such differences.[24]

Furthermore, as mentioned, it is known that normal cells in tissue culture have a finite life span of approximately 50 doublings. After this point cellular growth slows and eventually stops. Where the "biological clock" resides is unknown. One cell line escapes this phenomenon and appears to have an infinite life span. This is the malignantly transformed tumor cell. Thus, understanding why normal cells are finite should lead to understanding of why some cells become malignant. Another cellular event of great interest and importance is the progressive loss of immunological function which occurs with age.[25] With aging there occurs an inability of T lymphocytes to maximally proliferate. In addition there occurs an increase in T lymphocytes with the ability to suppress other immunological cells. Finally, the number of normal T lymphocytes decreases with age. This may not only explain the predisposition to infection that occurs with age, but it may also suggest that decreased immunological surveillance leads to the development of malignant clones of cells within the body. In fact, the progressive weakening of the thymus-dependent immune system has led to the suggestion that the thymus itself serves as an "organ clock" to determine longevity.[26]

Other questions relative to the determination of aging include the following. What are the specific genes that control aging? What are the mechanisms by which mutagenesis of cells occurs? What controls the rates and mechanisms of synthesis of nucleic acids, cellular enzymes, structural proteins and cell membranes? What are the mechanisms by which cells are damaged and how does repair take place? What role do slow or latent viruses play in biological aging?

How Will We Explore the Cellular Basis of Aging?

Aging is an extremely active area of investigation and many approaches are currently being used. Animal colonies allow us to study the process of aging in a telescoped time frame within an environment protected from external insult. These colonies offer a means by which perplexing and fascinating observations of aging may be studied. For instance, it has been found that experimental animals fed a calorically restricted diet live appreciably longer than animals allowed free access to food.[27] Why this occurs is unknown.

Tissue culture is a technique by which the basic cellular function itself may be investigated. Changes in metabolism, alterations of cell morphology and the effect of potentially damaging agents both within and external to the cell may be studied. With techniques of recombinant DNA the genetic information of the cell itself may be probed and its regulation investigated. For instance, it has been found that the introduction of the sarcoma virus gene into normal cells endows them with immortality.[28] The exact functional method by which this occurs remains to be elucidated.

Finally, certain "model diseases" are being utilized as methods to understand many phenomena including aging. Syndromes of premature aging include Hutchinson-Gilford progeria, Werner's syndrome and Hallerman-Streiff syndrome. Furthermore, one of the most facinating aspects of Down's syndrome is its association with premature aging.[29] It has been noted that persons with Down's syndrome who survive into the later decades of life tend to die younger than other persons with mental handicaps. In addition, in such adults with Down's syndrome a progressive dementia develops superimposed upon their amentia. Clinically and pathologically this closely resembles the finding in Alzheimer's disease.[30] This association between Down's syndrome and senility is made even more intriguing by the epidemiological demonstration of the familial clustering of Alzheimer's disease, malignancy and birth of children with Down's syndrome.[31]

It is possible that the relationship between aging and Down's syndrome may also extend to changes in immunological function. Disorders of immune function occur in both conditions. An imbalance of resting levels of cyclic nucleotides cyclic adenosine 3′,5′-monophosphate (CAMP) and cyclic guanosine 3′,5′-monophasphate (CGMP) and their generating enzymes has been found in T cells of both normal aged patients and those with Down's syndrome.[32] It is speculated that this finding may help to explain immune dysfunction that occurs with aging and the increased incidence of infection in patients with Down's syndrome.

Since this premature senility and changes in immunological function in Down's syndrome appear to be entirely due to the excess of a particular portion of chromosome 21 (the distal q22 band),[33] it is reasonable to conclude that if one could understand the nature of this genetic information then one would have insight into why premature aging occurs in patients with Down's syndrome. This information would have relevance to our understanding of aging in general.

Thus, while the cellular basis of aging still remains highly speculative, excellent theories exist from which rational experiments are currently being conducted. The techniques of modern day biology are allowing such investigations to be carried out at a rate faster than any other time in history. These studies will allow better strategies for caring for the elderly and perhaps increasing human longevity. Whether or not biogerontology will allow us to "tamper with our biological clocks" is at best uncertain.[34] It can be envisioned that decrease in damage to the cell would allow us to live a full life expectancy and then die suddenly in the ninth decade when our genetic time "runs out." Perhaps we will be able to even reset the clock. But this would certainly lead to further problems. Should the clock be allowed to run longer? Should the clock be reset at a particular development stage? If so, where? The period of maximal production and enjoyment can occur throughout human life.[35] Because of the potential of scientific inquiry to lead to understanding of biological phenomena, the day may come when such questions have more than just potential relevance.

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Special Article

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The International System of Units (SI) and Medicine

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A major international movement is in progress to extend metrication using the International System of Units. Significantly involved is the field of medicine. Extensive changes adopted abroad now appear in foreign medical literature, and physicians in the United States commonly are unprepared to interpret medical information from abroad because the data are reported in unfamiliar terms. The system has broad immediate and future implications to American physicians.

THE BRITISH IMPERIAL SYSTEM OF WEIGHTS, which is now used in the United States, originated from a variety of ancient cultures. The awkward base number 12 is Roman in origin. The yard was established by royal decree as the distance from the tip of the nose to the end of the thumb of King Henry I. The inch was based on the size of three grains of barley. Other equally illogically derived units eventually evolved into the irrational English system.[1]

The metric system, by contrast, with its base 10 or decimal system derived its units of mass and volume from its units of length, thus correlating its basic units. The need for further refinement of metrics into a single worldwide and interdisciplinary system of measurements led to the development of the International System of Units (le Système International d'Unités), with the international abbreviation SI. This has been referred to as "the modern metric system" and is said to complete the process of metrication.[2]

The Metric Conversion Act of 1975 passed by the United States Congress states, "It is therefore declared that the policy of the United States shall be to coordinate and plan the increasing use of the metric system. . . ."[3] This is intended to be voluntary with no specific deadline mandated. The term metric system as used in the act refers to SI.

The International System of Units

SI is a system of "base units" and "derived units" and their interrelationships. Seven base units and two supplementary units have been adopted (Table 1). Each unit can be defined in specific terms. The mole, for example, is the amount of substance that contains as many elementary entities as there are atoms in 0.012 kilograms of carbon 12. Base units are multiplied and divided to form derived units (Table 2). The newton (the SI unit for force), for example, is derived from three base units according to the expression $m \cdot kg \cdot s^{-2}$. Derivation promotes calcu-

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lation and understanding. Table 3 lists the prefixes denoting multiples of SI units.

Although both mass concentration (grams per liter) and substance concentration (moles per liter) are recognized in the SI system, there are certain purported advantages to recording data in substance concentration. Certain biological relations between blood constituents may be made clear when measurement is on the basis of their relative number (moles). Such relations may be masked by usage of mass concentration but may be better visualized in molar terms. Consider, for example, an unconjugated bilirubin concentration of 0.4 mg per dl and a serum albumin of 4.0 grams per dl. The concentration of bilirubin might appear to be 1/10,000 of that of albumin. In molar terms, however, there is only a 100-fold difference. The same concentrations are 6.8 and 620 μmol per liter, respectively. A serum bilirubin concentration of 20 mg per dl, which is a level of clinical importance in neonatology, is 340 μmol per liter, or more than half the concentration of albumin in this example.[4]

A more familiar example concerns the reporting of electrolytes. Sodium, potassium, chloride and carbon dioxide are reported in milliequivalents. The divalent ions, calcium and magnesium, are often expressed as mg per dl. It is difficult to understand ionic balance when diverse terminology is used. SI would create consistency.

Advantages

The present method by which values are reported by medical laboratories is disorganized. Physicians are accustomed to a nonsystem of units that developed over many years with little planning or logic. As a result, it is necessary to memorize normal limits as well as the particular unit involved for an enormous number of indi-

TABLE 1.—*SI Base Units*

Quantity	*Name*	*Symbol*
Length	Meter (metre)*	m
Mass	Kilogram	kg
Time	Second	s
Electric current	Ampere	A
Thermodynamic temperature†	Kelvin	K
Amount of substance	Mole	mol
Luminous intensity	Candela	cd
Supplementary units		
Plane angle	Radian	rad
Solid angle	Steradian	sr

*Both spellings acceptable.

†The Kelvin (the unit for thermodynamic temperature), not the degree Celsius, is in fact the SI unit for temperature. Their scale origins differ, but the degree Celsius equals the Kelvin in magnitude; thus, a rise in body temperature of 1.0 K is equivalent to a rise of 1.0°C, 0°C is defined as 273.15 K, therefore 98.6°F = 37°C = 310.15 K. The Celsius temperature scale (formerly called centigrade) is used for most medical and commercial purposes.

TABLE 3.—*SI Prefixes**

Factor	*Prefix Name*	*Prefix Symbol*	*Factor*	*Prefix Name*	*Prefix Symbol*
10^{18}	exa-	E	10^{-18}	atto-	a
10^{15}	peta-	P	10^{-15}	femto-	f
10^{12}	tera-	T	10^{-12}	pico-	p
10^{9}	giga-	G	10^{-9}	nano-	n
10^{6}	mega-	M	10^{-6}	micro-	μ
10^{3}	kilo-	k	10^{-3}	milli-	m
10^{2}	hecto-	h	10^{-2}	centi-	c
10^{1}	deca-	da	10^{-1}	deci-	d

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TABLE 2.—*Some SI Derived Units**

Quantity	*Name*	*Symbol*
Area	Square meter	m^2
Volume	Cubic meter	m^3
Velocity	Meter per second	m/s
Wave number	1 per meter	m^{-1}
Density, mass density	Kilogram per cubic meter	kg/m^3
Concentration (amount of substance)	Mole per cubic meter	mol/m^3
Activity (radioactive)	1 per second	s^{-1}
Specific volume	Cubic meter per kilogram	m^3/kg
Luminance	Candela per square meter	cd/m^2
Frequency	Hertz	$Hz = s^{-1}$
Force	Newton	$N = m \cdot kg \cdot s^{-2}$
Pressure	Pascal	$Pa = N/m^2 = m^{-1} \cdot kg \cdot s^{-2}$
Energy, quantity of heat, work	Joule	$J = N \cdot m = m^2 \cdot kg \cdot s^{-2}$
Power	Watt	$W = J/s = m^2 \cdot kg \cdot s^{-3}$
Electric potential, potential difference, electromotive force	Volt	$V = W/A = m^2 \cdot kg \cdot s^{-3} \cdot A^{-1}$
Electric resistance	Ohm	$\Omega = V/A = m^2 \cdot kg \cdot s^{-3} \cdot A^{-2}$

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vidual laboratory determinations, or take time to review this information on each occasion.

To further obfuscate the situation, normal limits vary from laboratory to laboratory. No master plan exists. SI, to a great extent, introduces uniformity to units: a few rules replace memorization. Not only is an attempt being made to standardize unitage, but ideas are coming forth to standardize normal values as well.[5]

A unifying proposal, then, is to express all concentrations as units per liter. (The multipliers are to be used in the numerator rather than the denominator.) Also proposed, when molecular weights are known, is the use of molecular units. Thus, most concentrations would be moles per liter or a multiple (see Table 4). The trade-off is as follows: although unitage would attain simplification and consistency, the change requires new numbers for almost every common chemical determination except electrolytes. Phased adoption has been suggested for the United States.[6] It has been recommended that conversion to molecular units not be automatic, but analytes be considered on an individual basis.[7]

One goal of metric conversion is that scientists of all varieties and nationalities might eventually communicate in the same units of measure. There would be an increase in ease and precision of scientific communication and avoidance of misunderstanding and error by international agreement. SI has the advantage of being logical, systematic, international and interdisciplinary.

Uncertainties and Problems

A potential disadvantage during introduction is danger to the patient by possible error engendered through unfamiliarity. For example, possible high and low serum values for digoxin are 5.0 mg per dl and 0.5 mg per dl, respectively. In SI terms, the second value becomes 5.0 mg per liter. Misreading this value as 5.0 mg per dl could lead to therapeutic error.[6] Two Canadian hospitals, however, reported conversion to SI units without harm to patients.[8] It has been suggested that medical publications use dual reporting for a period of time, using both SI and traditional units as clinicians learn the system.

Two of the SI-derived units relating to medicine are at present unknown to most clinicians. It is recommended that the joule replace the calorie in

TABLE 4.—*Some Factors for Converting Clinical Laboratory Concentration Data from Conventional to SI Molar Units**

Component	*Conventional Units*	*× Factor*	*= in SI Units*
Albumin	grams/dl	10.0	grams/liter
Bicarbonate	mM	1.0	mmol/liter
Bilirubin	mg/dl	17.1	μmol/liter
Calcium	mg/dl	0.25	mmol/liter
	mEq/liter	0.5	
Chloride	mEq/liter	1.0	mmol/liter
Cholesterol	mg/dl	0.026	mmol/liter
Creatinine	mg/dl	88.4	μmol/liter
Globulins	grams/dl	10.0	grams/liter
Glucose	mg/dl	0.055	mmol/liter
Iron	μg/dl	0.179	μmol/liter
Phosphorus	mg/dl	0.323	mmol/liter
Potassium	mEq/liter	1.0	mmol/liter
Protein, total	grams/dl	10.0	grams/liter
Sodium	mEq/liter	1.0	mmol/liter
Thyroxine	μg/dl	13.0	nmol/liter
Triglyceride	mg/dl	0.011	mmol/liter
Urea nitrogen	mg/dl	0.357	mmol/liter
Uric acid	mg/dl	0.059	mmol/liter
Complete blood count (CBC):			
Hematocrit	%	0.01	
Hemoglobin	grams/dl	10.0	grams/liter
Erythrocyte count	$10^6/\mu l$	10^6	10^{12}/liter
Leukocyte count	$10^3/\mu l$	10^6	10^9/liter
Erythrocyte indices:			
Mean corpuscular volume	cubic microns	1.0	fl
Mean corpuscular hemoglobin	pg	1.0	pg

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TABLE 5.—*Units and Conversion Factors for Quantities Used in the Clinical Laboratory**

Quantity	Conventional Unit: Name	Conventional Unit: Symbol	× Factor	= in SI Units: Name	= in SI Units: Symbol
Energy, work	Calorie	cal	4.187	Joule	J
Frequency	Per minute	min^{-1}	0.0167	Hertz (per second)	$Hz(s^{-1})$
Power	Kilocalorie per minute	kcal/min	69.8	Watt	W
	Horse power (metric)	HP	0.736	Kilowatt	kW
Radiation units:					
Absorbed dose	Rad	rd	0.01	Gray	Gy
Equivalent absorbed dose	Rem	rem	0.01	Joule per kilogram	J/kg
Radioactivity	Curie	Ci	37.0	Giga becquerel	GBq
	Roentgen	R	0.258	Millicoulomb per kilogram	mC/kg
Pressure	Millimeter of mercury	mm Hg	0.133	Kilopascal	kPa

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nutrition and dietetics. One calorie equals 4.184 J; therefore, a 1,000-calorie diet equals a 4.18 kilojoule diet.

Equally unfamiliar is the pascal, the SI unit of pressure. Blood pressures are now recorded in a metric unit, the millimeter of mercury (or torr). The pascal ($kg \cdot m^{-1} \cdot s^{-2}$ or the newton per square meter) is proposed to replace all other pressure units. Although too small for conventional clinical use, the kilopascal (10^3 pascal) has an appropriate magnitude. A kPa is equal to 7.5006 mm of mercury. A blood pressure of 130/80 would, therefore, be approximately 17/11 kPa. Retention of mm of mercury in the United States for the present has been recommended.[7]

An especially perplexing problem is the measurement of enzymatic activity. The previously introduced international unit is defined as the amount of enzyme that will catalyze the transformation of 1 micromole of substrate per minute under standard conditions. Acceptance of this unit has been slow, and many conventional units are still used. To conform with SI, a new base unit for enzymatic activity named the katal (one mole per second) has recently been proposed.

There is in use, in measuring enzymes, a wide variety of methods as well as conditions, such as pH and temperature. Attempts are being made at the international level to standardize assay conditions. Commonly, the mass and purity of many proteins are unknown, thus compounding the problem.

A recent survey showed extensive worldwide acceptance of SI units in medicine, especially the molar concentrations. However, in most countries the katal has not been adopted, protein is usually measured in grams per liter, mm of mercury is preferred to kPa and pH is preferred to nmol per liter as a measure of hydrogen ion concentration. Most countries reported the change to new units caused little trouble.[9]

Current Efforts

The American National Metric Council (ANMC) assumed the herculean task of gaining consensus in metrication by involving multiple scientific disciplines, consumers and industry simultaneously. The Medical and Health Coordinating Group of the ANMC is being organized with William R. Barclay, MD, as chairman. A wide variety of medical specialties and health organizations are being invited to participate in developing consensus regarding metrication in medicine.

Use of SI

Excellent and extensive reviews of the details of SI exist, including conversion tables and guidelines for usage.[2,10,11] Tables 4 and 5 summarize selected conversion data for items of common interest in medicine.

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in memoriam

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LEVINE, GERALD D., San Francisco. Died August 31, 1981, at Stanford Hospital of lymphoma, aged 43. Graduate of the Faculty of Medicine University of Cape Town, South Africa, 1961. Licensed in California in 1973. Dr. Levine was a member of the San Francisco Medical Society.

LORENZ, THOMAS M., Chico. Died March 16, 1981, aged 32. Graduate of the University of of California, San Francisco, School of Medicine, 1973. Licensed in California in 1973. Dr. Lorenz was a member of the Butte-Glenn Medical Society.

MICHLER, RAYMOND R., Napa. Died August 5, 1981, in Napa, aged 57. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1949. Licensed in California in 1949. Dr. Michler was a retired member of the Napa County Medical Society.

NATOLI, WILLIAM J., Redwood City. Died August 18, 1981, in the Trinity Alps near Redding of myocardial infarction, aged 60. Graduate of the University of Rochester School of Medicine and Dentistry, 1946. Licensed in California in 1941. Dr. Natoli was a member of the San Mateo County Medical Society.

Utah State Medical Association

ORTON, THOMAS KENNETH, Salt Lake City. Died August 11, 1981, in Alpine, Utah, aged 48. Graduate of the University of Maryland School of Medicine, Baltimore, 1962. Licensed in Utah in 1963. Dr. Orton was a member of the Salt Lake County Medical Society.

Washington State Medical Association

ANDERSON, CHARLES E., JR., Spokane. Died November 15, 1980, in Spokane, aged 56. Graduate of the University of Illinois College of Medicine, Chicago, 1948. Licensed in Washington in 1954. Dr. Anderson was a member of the Spokane County Medical Society.

BERTOLDI, ERMAND J., Everett. Died in September 1981 in Everett of brain tumor, aged 56. Graduate of the Creighton University School of Medicine, Omaha, 1954. Licensed in Washington in 1955. Dr. Bertoldi was a member of the Snohomish County Medical Society.

PERRY, ALMERON THOMAS, Spokane. Died July 24, 1981, in Spokane, aged 72. Graduate of the University of Oregon Medical School, Portland, 1943. Licensed in Washington in 1944. Dr. Perry was a retired member of the Spokane County Medical Society.

ROSELLINI, LEO J., Seattle. Died July 28, 1981, in Seattle, aged 71. Graduate of the Creighton University School of Medicine, Omaha, 1937. Licensed in Washington in 1938. Dr. Rosellini was a member of the King County Medical Society.

CONSULTANTS FOR *The Western Journal of Medicine in 1981*

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4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*
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Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications

Pregnancy Category C Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2 5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters Topical doses (5 gm/kg first two days, then 2 5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities There are no adequate and well controlled studies in pregnant women Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide) This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm The medication is expelled by spontaneous voiding It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained Thereafter, time intervals between therapy may be increased appropriately

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

In patients with severe interstital cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia (Saddle block has been suggested)

HOW SUPPLIED

Bottles contain 50 ml of sterile and pyrogen-free RIMSO® - 50 (50% w/w dimethyl sulfoxide aqueous solution)
Dimethyl sulfoxide is clear and colorless
Protect from strong light
Store at room temperature (50° to 86°F) (15° to 30°C)
Do not autoclave
NDC # 0433-0433-05

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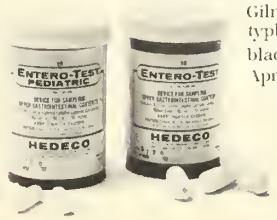

References:

Rosenthal, P., and Liebman, W.M: Comparative study of stool examinations, duodenal aspiration, and pediatric Entero-Test for giardiasis in children. *J. PEDIAT. 96:* 278 (Feb.) 1980.

Thomas, G. E., et al: Use of the Entero-Test duodenal capsule in the diagnosis of giardiasis. *South Afr. Med J. 48:* 2219, 1974.

Lopez, M. E., et al: Infeccion duodeno-yeyunal en el niño con desnutrician energetico-proteimica. *Rev. Med. Hosp. Nat. Niños 13:* 53, 1978.

Gilman, R. H: Identification of gall typhoid carriers by a string bladder device. *The Lancet:* April 14, p. 795, 1979.

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(Continued from Page 31)

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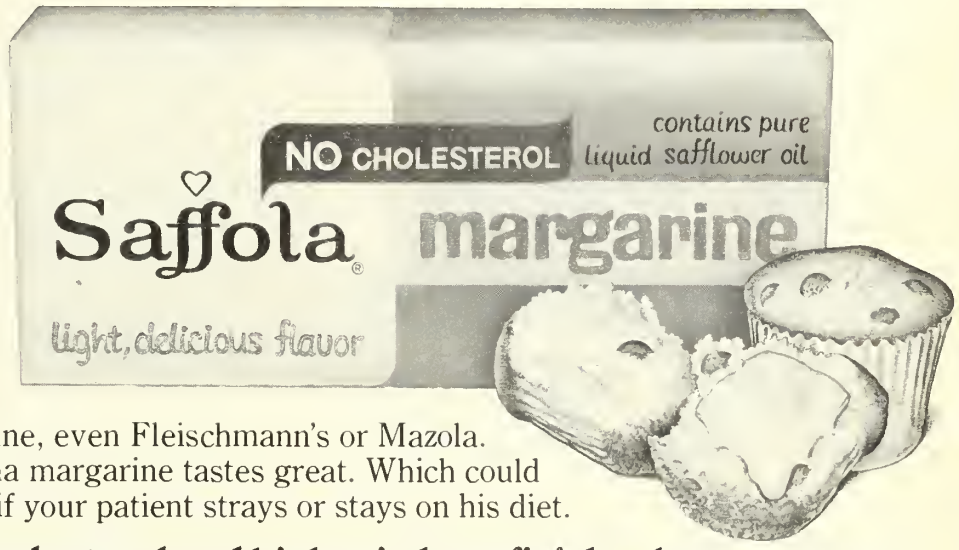

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CANCER CHEMOTHERAPY: Treatment and Care—Mary Kathryn Knobf, RN, BS, Oncology Nurse-Clinician, Section of Medical Oncology, Yale University School of Medicine; Keith P. Lewis, RPh, Oncology Clinical Pharmacist, Section of Medical Oncology, Yale University School of Medicine; David S. Fischer, MD, Clinical Professor of Medicine, Yale University School of Medicine, Diplomate in Internal Medicine. Hematology and Medical Oncology; Wendy R. Schneider, RN, MSN, Oncology Nurse Specialist, Section of Oncology, New York University Medical Center; and Deborah Welch, RN, MSN, Oncology Clinical Specialist, Roger Williams General Hospital—Edited by Marion E. Morra, MA, Communications Manager, Yale Comprehensive Cancer Center. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 306 pages, $24.95.

CARDIAC ARRHYTHMIAS—A Decade of Progress—Edited by Donald C. Harrison, MD, William G. Irwin Professor, Chief, Division of Cardiology, Stanford University School of Medicine, Stanford, California; Associate Editors: Jay W. Mason, MD; Harry A. Miller and Roger A. Winkle, MD. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 697 pages, $45.00.

CESAREAN BIRTH: A Couple's Guide for Decision and Preparation—Kathleen Mitchell and Marty Nason, RN. Harbor Publishing, 1668 Lombard Street, San Francisco (94123), 1981. 213 pages, $12.95 (hardbound), $9.95 (paperback).

DESIGNING AND BUILDING YOUR OWN PROFESSIONAL OFFICE—Murray Schwartz, DDS, Clinical Professor and Director of Undergraduate Periodontics, Columbia University School of Dental and Oral Surgery, private practice, Nyack, NY; Foreword by Mark S. Masch, MD, private practice, Upper Nyack, NY. Medical Economics Books (DPRH1), Box 157, Florence, KY (41042), 1981. 319 pages, $22.50, plus $1.25 handling charge (payment should accompany orders).

DORLAND'S ILLUSTRATED DICTIONARY—Twenty-sixth Edition.—W. B. Saunders Company, West Weshington Square, Philadelphia, PA (19105), 1981. 1,485 pages, 240 illustrations, $32.50, standard; $37.50, thumb-indexed.

DRUG ABUSE: A Guide for the Primary Care Physician—Department of Mental Health, American Medical Association, Bonnie Baird Wilford, Assistant Director. American Medical Association. Chicago, 1981, 335 pages. Available from: Order Department OP-323, American Medical Association, P.O. Box 821, Monroe, WI 53566, $15, plus $2 per order for handling.

THE FERTILITY FALLACY—Sexuality in the Post-Pill Age—Lynn S. Baker, MD, Resident in Psychiatry, University of California, Los Angeles, Neuropsychiatric Institute. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1981. 264 pages, $11.95. In the US distributed to the trade by Holt, Rinehart and Winston, 383 Madison Avenue, New York, NY 10017.

GYNECOLOGIC ONCOLOGY—Edited by Samuel C. Ballon, MD, CM, Associate Professor of Gynecology and Obstetrics, Director, Section of Gynecologic Oncology, Stanford University School of Medicine, Stanford, California—in the series: CONTROVERSIES IN CANCER TREATMENT, Harvey A. Gilbert, MD, Series Editor. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 487 pages, $49.95.

HARPER'S REVIEW OF BIOCHEMISTRY—Eighteenth Edition (Former title: REVIEW OF PHYSIOLOGICAL CHEMISTRY)—David W. Martin, Jr, MD, Professor of Medicine and Biochemistry, University of California, San Francisco, Investigator, Howard Hughes Medical Institute; Peter A. Mayes, PhD, DSc, Reader in Biochemistry, Royal Veterinary College, University of London; Victor W. Rodwell, PhD, Professor of Biochemistry, Purdue University, Lafayette, Indiana, and associate authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 614 pages, $18.00.

HE TOLD ME NOT TO TELL—Prepared by King County Rape Relief volunteers and staff. King County Rape Relief, 305 South 43rd, Renton, WA (98055), 1979. 28 pages, single copies for preview, $1.50. Bulk rates available. Washington State residents add 5.4% sales tax.

MANUAL OF ALLERGY AND IMMUNOLOGY: Diagnosis and Therapy—Edited by Glenn J. Lawlor, Jr, MD, Assistant Clinical Professor of Pediatrics, UCLA School of Medicine, Director, Allergy Clinic, UCLA Student Health Service, UCLA Center for the Health Sciences, Los Angeles; and Thomas J. Fischer, MD, Assistant Professor of Pediatrics, University of Cincinnati College of Medicine, Director, Division of Allergy/Immunology, Children's Hospital Medical Center, Cincinnati. Little, Brown and Company, 34 Beacon St., Boston, MA (02106), 1981. 504 pages, $14.95.

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

MEDICAL ONCOLOGY—Edited by Michael B. Van Scoy-Mosher, MD, Clinical Assistant Professor, University of Southern California Cancer Center; Attending Physician, Cedars-Sinai Medical Center, Los Angeles—in the series: CONTROVERSIES IN CANCER TREATMENT, Harvey A. Gilbert, MD, Series Editor. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1981. 467 pages, $49.95.

NOSOCOMIAL INFECTIONS—Edited by Richard E. Dixon, MD, Director, Department of Medicine, Helene Fuld Medical Center, Trenton, New Jersey, and Associate Clinical Professor of Medicine, Hahnemann Medical College, Philadelphia. Yorke Medical Books, 666 Fifth Avenue, New York, NY (10019), 1981. 326 pages, $29.50 (clothbound); $19.50 (paperbound).

PATHOPHYSIOLOGY: The Biological Principles of Disease—Editors: Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine, University of California, San Francisco; and Samuel O. Thier, MD, David Paige Smith Professor and Chairman, Department of Internal Medicine, Yale University School of Medicine—Volume I of INTERNATIONAL TEXTBOOK OF MEDICINE. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1981. 1,918 pages, $65.00 US; $78.00 Canada.

THE PHYSICIANS' DRUG MANUAL—Prescription and Nonprescription Drugs—Editors: Rubin Bressler, MD, Professor and Head, Departments of Medicine and Pharmacology, University of Arizona Health Sciences Center; Morton D. Bogdonoff, MD, Professor of Medicine, Cornell University College of Medicine; and Genell J. Subak-Sharpe, MS, Vice-President, Biomedical Information Corporation, New York. Doubleday & Company, Inc., 245 Park Avenue, New York, NY (10017), 1981. 1,213 pages, $17.95; $19.95 (thumb-indexed).

PRESCRIBER'S HANDBOOK OF THERAPEUTIC DRUGS—Harry Swartz, MD, Medical Economics Books, Box 157, Florence, KY (41042), 1981. 192 pages, $15.95, plus $1.25 handling charge.

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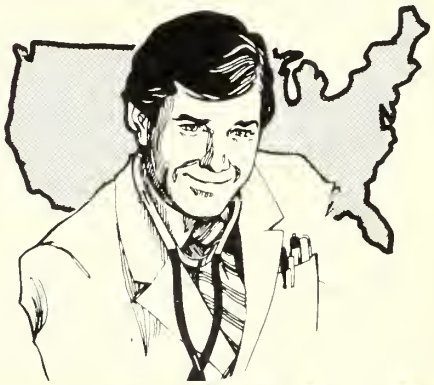

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(Continued from Page 23)

March 19-20—**Non-Invasive Cardiology Conference.** Clairemont Community Hospital at Sheraton Harbor Island Hotel, San Diego. Friday-Saturday. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

March 21-24—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Wednesday.

March 22-April 2—**30th Annual Review of Internal Medicine.** USC. 12 days.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** UCSD at Hilton, San Diego. Monday-Friday. 40 hrs.

April-June—**Allergy/Immunology for the Practicing Internist.** UCLA. Wednesday evenings.

April 1-3—**Asthma Update—1982.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 1-4—**Principles in the Practice of Allergic Diseases in Adults and Children.** UCD at Del Monte Hyatt, Monterey. Thursday-Sunday.

April 3—**Clinics in Medicine—Cardiology.** PMC. Saturday. 3 hrs. $40.

April 14—**Cardiology Update 1982.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

April 23-30—**Dermatology.** UCD. One week.

May 6-7—**Advances in Infectious Diseases.** UCSF. Thursday-Friday. 14 hrs. $170.

May 15—**Clinics in Medicine—Gastroenterology.** PMC. Saturday. 3 hrs. $40.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Bonaventure Hotel, Los Angeles. Saturday-Tuesday. 30 hrs. $35, members; $100, nonmembers. Contact: S. R. Iannotta, Exec. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 17-21—**Advances in Internal Medicine.** UCSF. Monday-Friday. 40 hrs. $375.

OBSTETRICS AND GYNECOLOGY

January 9-16—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui. One week. $395.

January 31-February 5—**Obstetrics and Gynecology Review and Update.** UCD at Hyatt, Lake Tahoe. Sunday-Tuesday.

February 4-6—**Practical Aspects of Gynecologic Urology, Intraepithelial Neoplasia, Infertility, and Ovum Transplantation.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 20 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 6-7—**Los Angeles OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $70. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 8-12—**37th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 14-17—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

March 20-24—**American Fertility Society.** See Of Interest To All, March 20-24.

March 27-April 3—**Obstetrics and Gynecology.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 2-3—**27th Annual T. Hart Baker, MD, Obstetrics and Gynecology Symposium.** Southern Calif. Permanente Medical Group at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Lilia M. Guerrero, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-4241.

May 10-12—**Recent Advances in OB/GYN.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 20 hrs. $300.

PEDIATRICS

January 16—**Pediatric Urology-Nephrology Seminar.** Western Section, American Urological Assn., at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Kathy De Santis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

January 31-February 2—**7th Annual Winter Ski and Study Symposium.** Calif. Chap. 2, American Academy of Pediatrics, at Mammoth Mountain. Sunday-Wednesday. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

February 6—**Pediatric Seminar: Congenital Anomalies.** Sutter Community Hospitals at Sutter Memorial Hospital, Sacramento. Saturday. 4 hrs. Contact: (916) 451-8898.

February 16-19—**Clinical Investigation.** See Of Interest to All, February 16-19.

March 12-14—**Combined Southern California Pediatric Postgraduate Program.** Calif. Chap. 2, American Academy of Pediatrics, at Palm Springs. Friday-Sunday. Contact: Calif. Chap. 2, AAP, P.O. Box 2134, Inglewood 90305.

March 17-19—**General Pediatrics.** American Academy of Pediatrics at Royal Lahaina Resort, Maui. Wednesday-Friday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

March 20-25—**American Academy of Pediatrics—Spring Session.** Sheraton Waikiki, Honolulu. Saturday-Thursday. Contact: Dept. of Education, AAP, P.O. Box 1034, Evanston, IL 60204. (312) 869-4255.

April 2-3—**Pediatric Topics.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

April 10-17—**Pediatric Emergencies.** See Emergency Medicine, April 10-17.

April 14—**Antibiotic Use in Pediatric Specialty Practice.** LLU. Wednesday. 4 hrs. $30.

April 22-24—**Advances in Pediatrics.** UCSF. Thursday-Saturday. 18 hrs. $250.

April 27-30—**7th Annual Symposium: Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Tuesday-Friday. 19 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 1—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 3-7—**12th Annual Review of Pediatrics.** USC. Monday-Friday. 32 hrs. $350.

May 29-31—**Challenges in Pediatrics.** Northern California Chapter, American Academy of Pediatrics, at Monterey. Saturday-Monday. Contact: David A. Zlotnick, MD, 3200 Middlefield Rd., Palo Alto 94306.

PSYCHIATRY

January 21-26—**Psychiatric Symposium.** Continuing Medical Education, Inc., and Western Medical Center at Maui Surf Resort, Maui. Thursday-Tuesday. 24 hrs. Contact: CME, Inc., 2030 E. 4th St., #113, Santa Ana 92705. (714) 547-5186.

January 24-29—**8th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday.

January 31-February 4—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 13-14—**Emotions in Health and Illness: Foundations of Clinical Practice.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. 12 hrs.

February 19-20—**Heinz Von Foerster on Cybernetics, Language and Understanding.** Mental Research Institute, Palo Alto. Friday-Saturday. 12 hrs. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 26-27—**The Use of Drugs in the Treatment of Patients With Psychiatric Disorders.** UCLA at VA Medical Center, Brentwood. Friday-Saturday. 6 hrs. $75.

February 27-28—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 12 hrs. $225.

March 12-14—**Short-Term Dynamic Psychotherapy.** UCSD at Hilton, San Diego. Friday-Sunday. 24 hrs. $275.

March 27—**Reconsiderations of Psychoanalytic Listening.** Southern California Psychoanalytic Society at Beverly Wilshire Hotel, Beverly Hills. Saturday. Contact: Mrs. Carol Ziff, Exec. Sec., So. Calif. Psychoanalytic Soc., 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

RADIOLOGY AND PATHOLOGY

January 20-22—**9th Annual Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 23 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., P.O. Box 1428, Long Beach 90801. (213) 595-3811.

January 29-31—**34th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Diane L. Johnson, L.A. Radiological Society, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

January 31-February 5—**4th Annual Winter Conference in the High Sierra—OB/GYN Imaging.** American College of Medical Imaging at Sahara, Lake Tahoe. Sunday-Friday. 25 hrs. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 3-5—**New Directions in Clinical Laboratory Assays: 4th Immunology Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 18 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 10—**Pulmonary Function Tests and Blood Gas Interpretation.** LLU. Wednesday. 4 hrs. $30.

March 3-5—**Sierra Radiology Conference—3rd Annual.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at North Lake Tahoe. Wednesday-Friday. 18 hrs. $265. Contact: Michael H. Reid, PhD, MD, Sac. Rad. Research and Ed. Fndn., P.O. Box 161112, Sacramento 95816.

March 4-5—**Pathology of Parasitic Infections.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 17 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 15-18—**International Workshop on Physics and Engineering in Medical Imaging.** UCI at Asilomar Conference Center, Pacific Grove. Monday-Thursday.

March 15-19—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $375.

March 24-26—**Gram Negative Organisms: An Approach to Identification.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. 20 hrs. Contact: Asst. Dir., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

April 11-15—**Postgraduate Course in Diagnostic Radiology.** Memorial Hospital Medical Center-UCI Center for Health Education at Disneyland Hotel, Anaheim. Sunday-Thursday. 24 hrs. Contact: Asst. Dir., UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 7-8—**Common Nervous System Pathology Diagnosis and Treatment.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 27 programs in all aspects of diagnostic radiology. Outstanding national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Radiology Postgraduate Ed. Section, UCSF, Dept. of Rad., Rm. M396, San Francisco 94143. (415) 666-5731, between 7:00 a.m. and 4:00 p.m.

SURGERY

January 14-16—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Canyon Hotel, Palm Springs. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

January 15-16—**Vitrectomy/Ocutome Workshop.** PMC. Friday-Saturday. 12 hrs.

January 16—**Pediatric Urology-Nephrology Seminar.** See Pediatrics, January 16.

January 18-22—**16th Otologic Surgery Course.** House Ear Institute, Los Angeles. Monday-Friday. Contact: Frederick H. Linthicum, Jr., MD, Dir. of Education, House Ear Inst., 256 S. Lake St., Los Angeles 90057. (213) 483-4431.

January 22-23—**7th Annual Postgraduate Course in Surgery.** UCD at Red Lion Inn, Sacramento. Friday-Saturday.

January 24-28—**Assembly in Surgery.** UCSD at Sheraton Harbor Island, San Diego. Sunday-Thursday.

January 30-February 6—**Office Urology for Urologists.** Univ. of Washington School of Medicine at Hyatt Regency, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 5-7—**National Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery and American Society for Dermatologic Surgery at Century Plaza, Los Angeles. Friday-Sunday. Contact: Drs. Richard Fleming and Toby Mayer, 9730 Wilshire Blvd., Suite 216, Beverly Hills 90212.

February 10-12—**Traumatic and Congenital Hand Surgery.** UCLA. Wednesday-Friday.

February 13-20—**Plastic Surgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

February 18-21—**Pathophysiology and Techniques of Cardiopulmonary Bypass: II.** Cardiothoracic Research and Education Fndn. and Vascular Disease Fndn. at Hilton on Mission Bay, San Diego. Thursday-Sunday. Contact: CREF, P.O. Box 33185, San Diego 92103.

February 28-March 4—**Lake Tahoe Vitreo-Retinal Symposium.** Retinal Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

March 1-5—**Surgical Forum.** Society of Graduate Surgeons at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 4-5—**13th Annual Lecture and Postgraduate Seminar—Pediatric Ophthalmology and Strabismus Update.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

March 12—**Male Infertility Seminar.** Western Section, American Urological Assn., at Marriott, Los Angeles. Friday.

Contact: Kathy De Santis, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

March 18-19—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

March 25-27—**Diagnosis and Treatment of Retinal, Macular and Vitreous Diseases.** Retina Research Fund of St. Mary's Hospital and Medical Center at Silverado Country Club, Napa. Thursday-Saturday. $225. Contact: Howard Schatz, MD, Retina Research Fund of St. Mary's Hosp., 450 Stanyan St., San Francisco 94117. (415) 921-4860.

March 28-31—**19th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Sunday-Wednesday.

March 29-April 2—**Management of Coronary Heart Disease: Medical, Surgical, Exercise.** See Medicine, March 29-April 2.

March 31-April 4—**10th Annual Symposium on Vascular Surgery.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday. $385.

April 2—**Anterior Vitrectomy—1982.** Sutter Community Hospitals at Sutter General Hospital, Sacramento. Friday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

April 15-17—**Postgraduate Course in General Surgery.** UCSF. Thursday-Saturday.

April 17-24—**Frontiers in Functional Neurosurgery.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 21-23—**American Intra-Ocular Implant Society.** Century Plaza, Los Angeles. Wednesday-Friday. Contact: AIOIS, P.O. Box 3140, Santa Monica 90403. (213) 829-7317.

April 23-24—**Vitrectomy Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

April 24-May 1—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 25 hrs. $325.

April 25-29—**American Association of Neurological Surgeons.** Honolulu. Sunday-Thursday. 40 hrs. Contact: Selene Patterson, AANS, 625 N. Michigan Ave., Suite 1519, Chicago 60611. (312) 944-4205.

May 12—**Surgical Subspecialties.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Secretary, Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

May 14-15—**Diagnostic Ocular and Orbital Ultrasound Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $125. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024.

OF INTEREST TO ALL PHYSICIANS

January 16—**Herpes Simplex: Clinical Practice and Research.** UCSF Cont. Ed. in Health Sciences at Fort Mason Conference Center, San Francisco. Saturday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

January 25-29—**Primary Care: Current Management of Common Office Problems.** UCSF. Monday-Friday.

January 28-30—**Modern Drug Therapy.** STAN. Thursday-Saturday. 13 hrs. $250.

January 29-30—**Symposium on Peripheral Vascular Disease.** Harbor-UCLA Medical Center at Disneyland Hotel, Anaheim. Friday-Saturday. 9½ hrs. $135. Contact: Judith Eldridge, Research and Education Inst., B-2 Annex, Harbor-UCLA Med. Ctr., 1124 W. Carson St., Torrance 90502. (213) 533-2847.

February 1-6—**Family Practice Refresher Course.** UCI at Marriott Hotel, Newport Beach. Monday-Saturday.

February 3-5—**Neurology for Non-Neurologists.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 6-7—**Immunology for the Family Physician.** UCLA. Saturday-Sunday.

February 7-12—**Winter Sports Injuries.** UCD at Ahwahnee Hotel, Yosemite. Sunday-Friday.

February 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

February 10-12—**32nd Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. $195. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2405.

February 13-14—**Emotions in Health and Illness.** See Psychiatry, February 13-14.

February 16-19—**Clinical Investigation.** Western Section of Am. Federation for Clinical Research, Western Soc. for Clinical Research, Western Section of Soc. for Investigative Dermatology, Western Soc. for Pediatric Research, and UCSF at Carmel. Tuesday-Friday. 20 hrs. $25, nonmembers + $10 for CME certificate. Contact: Allen D. Cooper, MD, Room S-069, Stanford Med Ctr., Stanford 94305.

February 16-June 8—**Family Practice.** USC. Tuesday evenings. $395.

February 18-19—**Hospital Epidemiology for Physicians and Infection Control Teams.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. Contact: Richard P. Henke, MD, Memorial Hosp., 2801 Atlantic Ave., Long Beach 90801. (213) 595-2431, ext. 23.

February 20-21—**Ninth Annual Family Practice Symposium.** So. Calif. Permanente Medical Group at Marriott, Anaheim. Saturday-Sunday. Contact: Dana Reisman, SCPMG, Dept. of Ed. and Research, 4747 Sunset Blvd., 4th Fl., Los Angeles 90027. (213) 667-7070.

February 22—**Symposium on Geriatric Medicine.** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Monday. 7 hrs. Contact: Barbara Davis, (916) 446-6667.

February 22-25—**Critical Care Medicine—20th Annual Symposium.** USC at MGM Grand, Las Vegas. Monday-Thursday. 28 hrs. $295.

February 22-26—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $325.

February 25-28—**8th Annual Basic, Intermediate and Advanced Workshops in Clinical Hypnosis.** UCI and Southern Calif. Society of Clinical Hypnosis at The Grand Hotel, Anaheim. Thursday-Sunday. 28 hrs. Contact: So. Calif. Soc. of Clinical Hypnosis, 4454 Van Nuys Blvd., Suite 215, Sherman Oaks 91403. (213) 872-3350.

March 1-2—**Treatment Issues in Geriatrics.** Western Gerontological Society and Washington State Psychiatric Assn. at Town and Country Hotel, San Diego. Monday-Tuesday. Contact: Barbara Freda, WGS, 785 Market St., Suite 1114, San Francisco 94103. (415) 543-2617.

March 5-6—**Advances in Alcoholism—Third Annual Symposium.** Raleigh Hills Foundation and American Medical Society on Alcoholism at Registry Hotel, Newport Beach. Friday-Saturday. $200. Contact: Kim Hilberg, Raleigh Hills Fndn., 17861 Cartwright Rd., Irvine 92714. (714) 641-1616.

March 5-11—**Annual Postgraduate Convention—Primary Care Update.** LLU School of Medicine Alumni Assn. at LLU. One week. Contact: Beverly Hardt, 11245 Anderson St., Suite 200, Loma Linda 92354. (714) 824-4633.

March 8-12—**Sports Medicine.** Northwestern Univ. Center for Sports Medicine at Maui. Monday-Friday. 25 hrs. Contact: Bates Noble, MD, Northwestern Univ. Ctr. for Sports Medicine, 303 E. Chicago Ave., Chicago 60611.

March 10—**Pain Management.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6-7 hrs. $35. Contact: Med. Staff Office, Enloe Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

March 10-13—**Optimal Health: A Guide for Practicing Physicians.** Scripps Clinic and Research Fndn. at La Costa Resort Hotel, Carlsbad. Wednesday-Saturday. 22 hrs. Contact:

Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

March 12-17—**California Medical Association—111th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 13-20—**Reproductive Endocrinology.** USC at Maui. One week. $395.

March 15-19—**Sports Medicine.** Ohio State Univ. and Univ. of Hawaii at Princess Kaiulani Hotel, Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Joy Lewis, Box CE-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 18-21—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $175.

March 19—**Diabetes and Nutrition Update.** UC and STAN at Hilton, San Francisco. Friday. Contact: UCD.

March 19-21—**In Pursuit of Wellness.** UCSF at Jack Tar Hotel, San Francisco. Friday-Sunday. $75. Contact: UCSF Cont. Ed. in Health Sciences, 1308 Third Ave., San Francisco 94143. (415) 666-2894.

March 20-24—**American Fertility Society—38th Annual Meeting and 15th Postgraduate Program.** MGM Grand, Las Vegas. Saturday-Wednesday. Contact: Herbert H. Thomas, MD, Med. Dir., AFS, 1608 13th Ave. S., Suite 101, Birmingham, AL 35256. (205) 933-7222.

March 20-27—**Medical Genetics for Health Professionals.** San Jose State University. One week. 15 hrs. Contact: Kate Wright-Rodgers, MPH, Cont. Ed., San Jose State Univ., Washington Square, San Jose 95192. (408) 277-3778.

March 27-April 3—**Otolaryngology for Non-Otolaryngologists.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 3-10—**Topics in Family Practice.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 10-17—**Management of Pain.** Univ. of Washington School of Medicine at Wailea Beach, Maui. One week. Contact: Univ. of WA Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

April 22-24—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 22-25—**Wound Management.** UCSD at Hilton, San Diego. Thursday-Sunday. 20 hrs.

May 1-5—**Medical Evaluation of the Preoperative Patient.** UCD at Del Monte Hyatt, Monterey. Saturday-Wednesday. 16 hrs. $250.

May 1-8—**Diagnostic and Therapeutic Skills.** USC at Hawaii. One week. 29 hrs. $425.

May 2-5—**American Medical Informatics Association Congress 82—First Annual Joint Conference.** AMIA, Soc. for Advanced Medical Systems, Soc. for Computer Medicine, Internat'l Health Evaluation Assn., Salutis Unitas, Univ. of Missouri-Columbia Health Care Technology Ctr., IL Conf. on Medical Information Systems, at Hyatt on Union Square, San Francisco. Sunday-Wednesday. Contact: M. F. Collen, MD, 3451 Piedmont Ave., Oakland 94611.

May 3-7—**Symposium on Non-Emergent Outpatient Care.** UCSD at Hilton, San Diego. Monday-Friday. 27 hrs. $325.

May 3-9—**Basic Diving Medicine.** UCSF at Fresno. One week. Contact: Vincent S. O'Hara, MD, VA Medical Center, 2615 E. Clinton, Fresno 93703. (209) 225-6100, ext. 345.

May 12—**Common Fractures.** LLU. Wednesday. 4 hrs. $30.

May 16-21—**Fingers-to-Toes: An Orthopedic Approach for the Family Physician.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Sunday-Friday. 40 hrs. $375.

May 22-23—**Conference on Health Problems Related to the Chinese in America.** Chinese Hospital and UCSF at Holiday Inn/Financial District, San Francisco. Saturday-Sunday. 12

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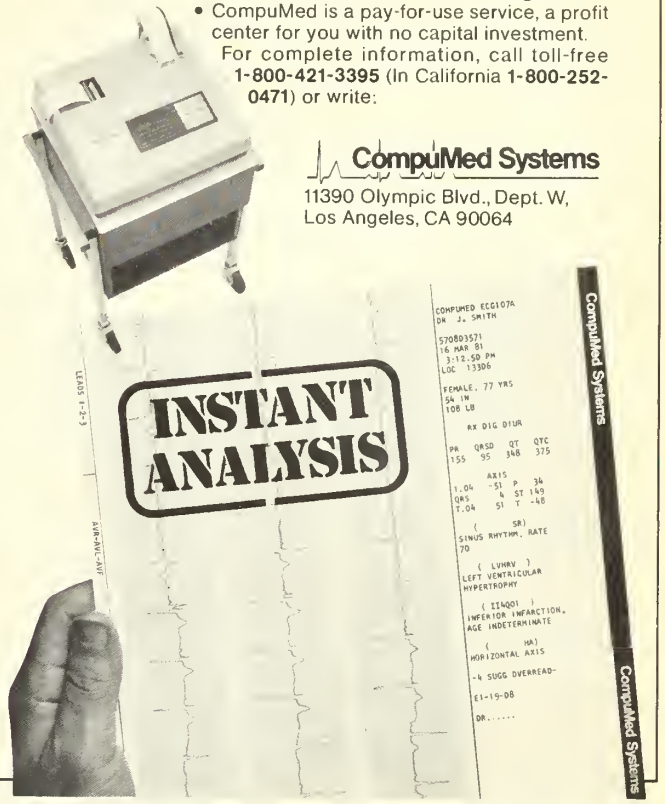

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Audio-Digest Foundation—A nonprofit subsidiary of CMA. Provides by subscription twice-a-month tape recorded summaries of leading national meetings and authoritative surveys of current literature. A catalog of lectures and panel discussions in all areas of medical practice is also available. Contact: Audio-Digest Foundation, 1577 E. Chevy Chase Dr., Glendale 91206.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

ALASKA

No courses announced.

IDAHO

See Washington Listings, February 13, March 6-13, and June 19-26.

MONTANA

March 20-March 27—**Pulmonary Diseases: A Practical Approach.** Big Sky. Saturday-Saturday. 20 Category I credit hours; also 20 AAFP Elective hours, and 20 ACEP hours. Fee: $260 for Physicians; $180 for Physicians Assistants, Interns and Residents. Contact: M. S. M. Watts, MD, Associate Dean and Director, University of California, San Francisco, Extended Programs in Medical Education, San Francisco, CA 94143. Telephone—For Registration: (415) 666-2894 or 666-2483; for Program Information: (415) 666-4251.

April 15-17—See Washington Listings.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information and requests for accreditation should be sent to the chairman of the CME Committee, New Mexico Medical Society, P.O. Box 9366, Albuquerque, NM 87119 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 247-0539.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 4-5—**Trauma Update '81.** Albuquerque. Friday-Saturday. Convention Center. 11 hours credit. Contact: Office of CME, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

December 11-12—**Annual Meeting New Mexico Chapter American College of Physicians and New Mexico Chapter American Society of Internal Medicine—Clinical Hematology and Oncology.** Albuquerque. Friday-Saturday. Veterans Administration Medical Center. 9 credit hours, also AAFP Prescribed. Contact: Robert Weiler, MD, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7178.

January 15—**Lythic Therapy Seminar.** Albuquerque. Friday. Savage Auditorium, Presbyterian Hospital Center. 4 credit hours, also AAFP. Contact: Office of Continuing Education, Presbyterian Hospital Center, 1101 Central SE, Albuquerque, NM 87102. (505) 841-1225.

February 22-26—**Taos Medical Symposium—Sports Medicine.** Taos. Monday-Friday. Kachina Lodge. 18 credit hours, also AAFP Prescribed. Contact: Dale A. Gray, MD, Taos Medical Symposium, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

February 26-28—**10th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 13 credit hours, also AAFP Prescribed. Contact: American Lung Association of New Mexico, 216 Truman NE, Albuquerque, NM 87108. (505) 265-0732.

March 8-10—**New Mexico Metabolism Seminar.** Taos. Monday-Thursday. Tennis Ranch. 15 credit hours. Contact: Martin J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

March 16-21—**Purgatory Medical Ski Symposium.** Durango, Colorado. Tuesday-Sunday. Iron Horse Resort & Convention Center. 28 credit hours, also AAFP Prescribed. Contact: David R. Holten, MD, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

March 30-31—**Base Station Physician Course.** Taos. Tuesday-Wednesday. Sagebrush Inn. 9 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, NM Chapter American College of Emergency Physicians, 6320 Palma Pl. NW, Albuquerque, NM 87120.

April 1-3—**New Mexico Chapter, American College of Emergency Physicians Meeting.** Taos. Thursday-Saturday. Sagebrush Inn. 18 credit hours, also AAFP Prescribed. Contact: Arleen L. Sadowsky, MD, President, 6320 Palma Pl. NW, Albuquerque, NM 87120.

May 5-7—**New Mexico Medical Society Annual Meeting.** Santa Fe. Wednesday-Friday. Hilton Inn. 10 credit hours, also AAFP. Contact: NMMS, PO Box 9366, Albuquerque, NM 87119. (505) 247-0539.

June 17-19—**Radiology for Family Physicians 1982—An Update.** Santa Fe. Thursday-Saturday. Symposia de Santa Fe. 15 credit hours, also AAFP Prescribed. Contact: Marcus J. Smith, MD PO Box 5175, Santa Fe, NM 87501. (505) 982-5218.

July 8-10—**25th Annual Meeting, New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8 credit hours. Contact: Walter J. Levy, MD, 465 St. Michael's Dr., Santa Fe, NM 87501. (505) 982-1911.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 247-0539 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 8-12—**Thirteenth Annual Family Practice Review.** Portland. Monday-Friday. Marriott Hotel. For additional information please contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

MKSAP V REVIEW

(Sponsors: Utah Region, American College of Physicians/Utah Society of International Medicine/University of Utah)
University Medical Center, Salt Lake City

October 1981-June 1982 (Ongoing)—Thursdays. 2 hrs. Fee: $160 (ACP non-members); $60 (ACP members). Contact: John Holbrook, MD (801) 581-7818.

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December 10-12—**Dilemmas of Ethics and Health: Informed Consent Conference** (Sponsor: University of Utah). Park City. Thursday-Saturday. 11 hrs. Fee: $175. Contact: Claire Turner (801) 581-5809.

January 3-9—**9th Annual Symposium on Clinical Echocardiography** (Sponsors: American College of Cardiology/University of Utah). Snowbird. Sunday-Saturday. 22.5 hrs. Fee: $200-$300. Contact: A. D. Hagen, MD (801) 350-1185.

January 11-23—**Perinatal/Neonatal Administrative Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Monday-Saturday. Salt Lake Marriott. 58 hrs. Fee: $100-$300. Contact: Jean Thornton, RN (801) 581-7085.

January 13-14—**Diabetes Update** (Sponsor: Regional Medical Education Center/VA Hospital). Salt Lake City. Thursday-Friday. Hotel Utah. 15 hrs. Fee: $50. Contact: Nancy Harrison (801) 582-1565, ext. 1100.

January 16-20—**Immune Consequences of Thermal and Traumatic Injury** (Sponsor: University of Utah). Snowbird. Saturday-Wednesday. 18 hrs. Fee: $245. Contact: Claire Turner (801) 581-7617.

January 22—**Anterior and Posterior Segment Photocoagulation** (Sponsor: University of Utah). Salt Lake City. Friday. Research Lecture Hall, UUMC. 6 hrs. Fee: $50. Contact: Mano Swartz, MD (801) 581-6384.

January 29-30—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

February 8-11—**11th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 32 hrs. Fee: $250. Contact: Linda Twitchell (801) 581-8633.

February 12-16—**27th Annual Postgraduate Course in Anesthesiology: Anesthesiology and the Lung** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hotel Utah. 17 hrs. Fee: $250. Contact: T. Stanley, MD (801) 581-6393.

February 15-19—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-day-Friday. Holiday Inn. 25 hrs. Fee: $300. Contact: John Matsen, MD (801) 581-5514.

February 20-23—**23rd Annual OB/GYN Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. The Yarrow. 14 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

February 20-27—**The Snowbird Conference on Modern Diagnostic Methods in Internal Medicine.** (Sponsors: George Washington University Medical Center, Washington, DC/ Academy of Continuing Medical Education, Salt Lake City). Snowbird. Saturday-Saturday. 15 hrs. Fee: $245 (Residents: $150). Contact: Gregg P. Thomas, CME Office, George Washington University Medical Center, 2300 Eye Street, NW, Washington, DC 20037. (202) 676-4285.

February 24-27—**Reproductive Endocrinology and Infertility Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. The Yarrow. 14.5 hrs. Fee: $275. Contact: David Engleberg (801) 581-3087.

March 1-3—**Common Problems in Pediatrics—Intermountain Pediatric Society Annual Scientific Meeting** (Sponsor: University of Utah). Salt Lake City. Monday-Wednesday. Little America. 15 hrs. Fee: $190. Contact: Jacque Bachtell (801) 581-3729.

March 1-5—**7th Annual Advances in Internal Medicine** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 6-13—**4th Annual Park City Radiology Conference** (Sponsor: University of Utah). Park City. Saturday-Saturday. Holiday Inn. 20 hrs. Fee: $290. Contact: P. Ruben Koehler, MD (801) 581-8188.

March 8-12—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 13-20—**First Annual Oculo-Plastic SRI Meeting** (Sponsor: University of Utah). Park City. Saturday-Saturday. 15 hrs. Fee: $225. Contact: Darrel Wolfley, MD (801) 363-3355.

March 15-19—**Second Annual Nutrition in Contemporary Medicine Course** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. Fee: $225. Contact: Jennifer Fossum (801) 581-3581.

March 18-19—**Infection Control Update—Rocky Mountain Infection Control Association (RMICA)** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America. 12 hrs. Fee: $75. Contact: Sego Matsumiya (801) 582-1565.

March 20-27—**Park City Dermatological Seminar** (Sponsor: Intermountain Dermatology Foundation [IDF]). Park City. Saturday-Saturday. Shadow Ridge Condo Hotel. 16 hrs. Fee: $250. Contact: IDF, 1151 East 3900 South, Salt Lake City 84117 (801) 268-0435.

March 24-25—**Genetics: Impact of Genetic Disorders on the Family** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. University of Utah Medical Center. 12 hrs. Fee: $50-$65. Contact: John Carey, MD, (801) 581-8943.

March 26-27—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Friday-Saturday. Hilton Inn. 16 hrs. Fee: $350. Contact: Tricia Harris, RN (801) 533-6435.

April 7-9—**Health Hazards of Minerals and Mining: 4th Annual Park City Environmental Health Conference** (Sponsors: University of Utah/Rocky Mountain Center for Occupational and Environmental Health). Park City. Monday-Wednesday. 24 hrs. Fee: $300. Contact: Katharine Blosch (801) 581-5710.

April 15-17—**First Annual Clinical Ophthalmology Meeting at Snowbird** (Sponsor: University of Utah). Snowbird. Tuesday-Thursday. 9 hrs. Fee: $50. Contact: Rebecca Olsen (801) 581-6384.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

December 10-11—**Aging and Elderly.** Seattle. Thursday-Friday. Washington Athletic Club. Contact: U/W.

December 10-12—**Cytology Continuing Education Workshop.** Spokane. Thursday-Saturday. Sacred Heart Medical Center. Contact: CME Harborview.

January 9-16—**(HAWAII) Endocrinology and Metabolism.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

January 14-15—**Sexual Disorders in Medical Practice.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 15—**Perspectives in Rheumatology and Clinical Immunology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

January 20—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

January 21-22—**Beta Block/Calcium Antagonists.** Seattle. Thursday-Friday. Seattle Hilton. Contact: U/W.

January 21-23—**Retina and Vitreous.** Seattle. Thursday-Saturday. Doubletree Plaza Hotel. Contact: Marcia Wahlman,

Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 28-29—**Financial Planning for Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

January 28-30—**(OREGON) Cytology Continuing Education Workshop.** Portland. Thursday-Saturday. Contact: CME Harborview.

January 30-February 6—**(HAWAII) Office Urology for Urologists.** Maui. Saturday-Saturday. Hyatt Regency. Contact U/W.

January 31-February 7—**(MEXICO) Surgical Management of Trauma.** Puerto Vallarta. Sunday-Sunday. Camino Real. Contact: U/W.

February 1—**Fifth Annual Cancer Conference.** Everett. Monday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

February 5-6—**Case Studies in Internal Medicine.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 6-13—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 12—**Nutrition in Hospitalized Patients.** Seattle. Friday. Park Hilton. Contact: U/W.

February 13-20—**(HAWAII) Plastic Surgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 13-20—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

February 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

February 20-27—**(HAWAII) Cardiology.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

February 24-26—**American College of Physicians: Clinical Topics in Pulmonary Disease.** Seattle. Wednesday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-27—**Stroke: Current Concepts.** Seattle. Thursday-Friday. Northwest Hospital. Contact: Marilyn Carlson, Northwest Hospital Education and Training Department, 1551 N. 120th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 26-28—**Cytology Continuing Education Workshop.** Seattle. Friday-Saturday. Northwest Hospital. Contact: CME Harborview.

February 27—**Behavioral Techniques in Primary Care.** Seattle. Saturday. Group Health Cooperative of Puget Sound. Contact: Ed Oshiro, Office of Medical Education, Group Health Cooperative of Puget Sound, 200 15th Avenue East, Seattle, WA 98112. (206) 326-7348.

March 1-2—**(CALIFORNIA) Washington State Psychiatric Association: Treatment Issues in Geriatrics.** San Diego. Monday-Tuesday. Town and Country Hotel. Contact: Barbara Freda, Western Gerontological Society, 785 Market Street, Suite 1114, San Francisco, CA 94103. (415) 543-2617.

March 1-2—**Computers in Continuing Education.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

March 4-5—**Gynecology for Primary MDs.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 6—**Handicapped Child.** Seattle. Saturday. Children's Orthopedic Hospital and Medical Center. Contact: U/W.

March 6-13—**(IDAHO)—Perinatal Critical Care.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

March 11-12—**Tacoma Academy of Internal Medicine—Annual Meeting.** Tacoma. Thursday-Friday. Contact: CME Pierce County.

March 11-12—**Holistic Medicine.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 17—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

March 18-19—**Depression and Anxiety.** Seattle. Thursday-Friday. U/W Health Sciences Bldg. Contact: U/W.

March 19-20—**Days of Pediatrics.** Tacoma. Friday-Saturday. Contact: CME Pierce County.

March 26-27—**Recombinant DNA for the Clinician.** Seattle. Friday-Saturday. U/W Health Science Bldg. Contact: U/W.

March 27-April 3—**(HAWAII) Obstetrics and Gynecology.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 27-April 3—**(HAWAII) Otolaryngology for Non-Otolaryngologists.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

March 29-April 9—**Rehabilitation Medicine Review.** Bellevue. Monday-Friday. Bellevue Hilton. Contact: U/W.

March 31—**Medicine and Civilization.** Seattle. Wednesday. U/W Health Sciences Building. Contact: U/W.

April 3-10—**(HAWAII) Topics in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 7, 14, 21, 28, May 5—**Medicine and Civilization.** Seattle. Wednesdays. U/W Health Sciences Building. Contact: U/W.

April 8—**Dermatology Conference.** Everett. Thursday. Everett Pacific Hotel. Contact: Sheri Lindquist, Medical Education Coordinator, PO Box 1147, Everett, WA 98206. (206) 258-6322.

April 9-10—**Management of Obesity: Scientific Approach.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

April 10—**Mason Clinic Day.** Seattle. Saturday. Virginia Mason Medical Center. Contact: VMMC.

April 10-17—**(HAWAII) Management of Pain.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 15-17—**(MONTANA) Cytology Continuing Education Workshop.** Billings. Thursday-Saturday. Contact: CME Harborview.

April 17-24—**(HAWAII) Frontiers in Functional Neurosurgery.** Maui. Saturday-Saturday. Wailea Beach. Contact: U/W.

April 21—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

April 22-23—**Vascular Diseases.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

April 28-30—**Children's Orthopedic Hospital and Medical Center 75th Anniversary.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

April 29—**Trauma.** Seattle. Thursday. Museum of History and Industry. Contact: U/W.

May 7—**The Foot.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-15—**Third Annual Cardiology Conference.** Tacoma. Thursday-Saturday. Contact: CME Pierce County.

May 14—**Medical Alumni.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

May 14-15—**Therapeutics in Common Medical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19—**Internal Medicine Review.** Spokane. Wednesday. Sacred Heart Medical Center. Contact: U/W.

May 20—**Estrogen Controversy.** Tacoma. Thursday. Contact: CME Pierce County.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101. (206) 223-6898.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: June 6-8, 1982, Chena Hot Springs.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. House of Delegates' Annual Meeting: May 28-29, 1982, The Pointe Resort, Phoenix.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 12-17, 1982, Disneyland Hotel, Anaheim.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: 1982—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: 1982—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 14-16, 1982, MGM Grand Hotel, Reno.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 5-7, 1982, Hilton Inn, Santa Fe.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: 1982—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: 1982—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Midwinter Seminar January 7-9, 1982, Teton Village, Jackson. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

May 21-22—**Topics in Emergency Room Medicine: The First 60 Minutes.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

May 27-28—**Current Concepts in Management of Joint Disease.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

June 11-12—**Common Minor Surgeries.** Seattle. Friday-Saturday. Park Hilton. Contact: U/W.

June 14-18—**Advances in Family Practice.** Seattle. Monday-Friday. Seattle Hilton. Contact: U/W.

June 17-19—**Medical Aspects of Dance.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact. U/W.

June 19-26—**(IDAHO) Radiology Northwest V.** Sun Valley. Saturday-Saturday. Elkhorn. Contact: U/W.

June 21-25—**Internal Medicine Review.** Seattle. Monday-Friday. Park Hilton. Contact: U/W.

June 23-27—**(OREGON) Ethics and History with Shakespeare.** Ashland. Wednesday-Sunday. Ashland Inn. Contact: U/W.

June 24-25—**EKG Interpretation and Arrythmias.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

WYOMING

January 7-9—**Wyoming Medical Society Midwinter Seminar.** Jackson. Thursday-Saturday. Teton Village. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82001. (307) 635-2424.

June 30-July 3—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne. WY 82001. (307) 635-2424.

See Washington listing, September 16-18, 1982.

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